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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(51) International Patent Classification <sup>6</sup> :</b><br><b>C07D 401/06, 403/06, A61K 31/445, 31/415</b>  | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 99/24421</b><br><b>(43) International Publication Date:</b> 20 May 1999 (20.05.99)  |
| <b>(21) International Application Number:</b> PCT/US98/23224<br><b>(22) International Filing Date:</b> 5 November 1998 (05.11.98)<br><b>(30) Priority Data:</b><br>08/965,754 7 November 1997 (07.11.97) US<br><b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</b><br>US 08/965,754 (CIP)<br>Filed on 7 November 1997 (07.11.97)<br><b>(71) Applicant (for all designated States except US):</b> SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).<br><b>(72) Inventors; and</b><br><b>(75) Inventors/Applicants (for US only):</b> VACCARO, Wayne, D. [US/US]; 1706 Westover Road, Yardley, PA (US). WOLIN, Ronald, L. [US/US]; 42 Heatherwood Lane, Bedminster, NJ 07921 (US). SOLOMON, Daniel, M. [US/US]; 9 Marshall Drive, Edison, NJ 08817 (US). ASLANIAN, Robert, G. [US/US]; 144 Philip Drive, Rockaway, NJ 07866 (US). PIWINSKI, John, J. [US/US]; 6 Saddle Ridge Drive,   |           | Lebanon, NJ 08833 (US). ROSENBLUM, Stuart, B. [-/US]; 16 Steven Terrace, West Orange, NJ 07052 (US).<br><b>(74) Agents:</b> JEANETTE, Henry, C. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).<br><b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).<br><b>Published</b><br><i>With international search report.</i> |
| <b>(54) Title:</b> IMIDAZOYLALKYL SUBSTITUTED WITH A FIVE, SIX OR SEVEN MEMBERED HETEROCYCLIC RING CONTAINING ONE NITROGEN ATOM<br><div style="text-align: center; margin: 20px 0;"> </div> <p style="text-align: right;">(I)</p>  |           |   |
| <b>(57) Abstract</b><br><p>Disclosed are compounds of Formula (I) or pharmaceutically acceptable salts or solvates thereof. Also disclosed are pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a Compound of Formula (I). Further disclosed is a method of treating allergy (for example asthma), inflammation, hypotension, raised intraocular pressure (such as glaucoma) i.e., a method of lowering intraocular pressure, sleeping disorders, states of hyper and hypo motility and acidic secretion of the gastrointestinal tract, hypo and hyperactivity of the central nervous system (for example, agitation and depression) and other CNS disorders (such as Alzheimer's, Schizophrenia, obesity and migraine) comprising administering an effective amount of a compound of Formula (I) to a patient in need of such treatment. Also disclosed are methods for treatment of upper airway allergic responses comprising administering a compound, or salt or solvate thereof, of Formula (I) in combination or admixture with a histamine H<sub>1</sub> receptor antagonist.</p> |           |   |

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**IMIDAZOYLALKYL SUBSTITUTED WITH A FIVE, SIX OR  
SEVEN MEMBERED HETEROCYCLIC RING CONTAINING ONE  
NITROGEN ATOM**

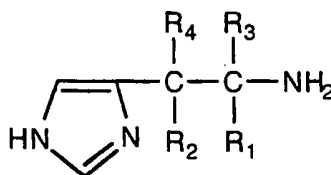
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**BACKGROUND**

H<sub>3</sub> receptor sites are known and are of current interest to those skilled in the art--for example, see: West, Jr. et al., "Biexponential Kinetics of (R)- $\alpha$ -[<sup>3</sup>H]Methylhistamine Binding to the Rat Brain H<sub>3</sub> Histamine Receptor", Journal of Neurochemistry, Vol. 55, No. 5, pp. 1612-1616, 1990; West, Jr. et al., "Identification of Two H<sub>3</sub>-Histamine Receptor Subtypes", Molecular Pharmacology, 38:610-613; and Korte et al., "Characterization and Tissue Distribution of H<sub>3</sub> Histamine Receptors in Guinea Pigs by N <sup>$\alpha$</sup> -Methylhistamine", Biochemical and Biophysical Research Communications, Vol. 168, No. 3, pp. 979-986.

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Arrang et al. in U.S. 4,767, 778 (Issued August 30, 1988) disclose a pharmaceutical composition containing a histamine derivative of the formula:



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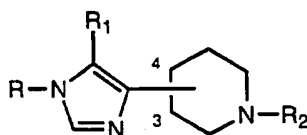
wherein each of R<sub>1</sub>, R<sub>2</sub>, and R<sub>4</sub>, represents a hydrogen or a methyl, or R<sub>1</sub> and R<sub>2</sub> taken together represent a methylene, and R<sub>3</sub> is a hydrogen, a methyl or a carboxy, with the proviso that R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are not simultaneously methyl groups. It is disclosed that the derivatives behave as complete agonists of the H<sub>3</sub> receptors in rat brain and produce a maximal inhibition of release identical to that induced by histamine

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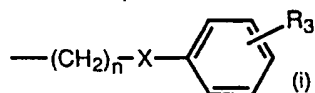
(approximately 60%). It is also disclosed that the histamine derivatives powerfully inhibit the release and synthesis of histamine by very selectively stimulating the H<sub>3</sub> receptors. Consequently, according to Arrang et al., the derivatives are likely to decrease histaminergic transmission in the digestive tract and in the nervous, cardiovascular and immune systems. Arrang et al. disclose that the derivatives can be used in therapy as a drug having sedative effects, as a sleep regulator, anticonvulsant, regulator of hypothalamic-hypophyseal secretion, antidepressant, and modulator of cerebral circulation. According to Arrang et al., inhibition of the release of inflammation messengers in various allergic conditions (e.g., asthma) is expected to result from stimulation of the H<sub>3</sub> receptors of the lung. It is further disclosed that the inhibition of release of gastric histamine is likely to exert antisecretory and anti ulcerative effects. According to Arrang et al., modification of release of the messengers of immune responses is likely to modulate the latter responses.

Derwent abstract 86-273706/42 for EP 0 197 840 discloses imidazole derivatives of the formula:

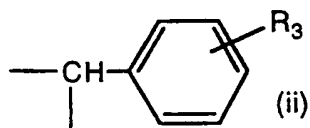


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wherein R<sub>1</sub> is H, methyl or ethyl; R is H or R<sub>2</sub>; and R<sub>2</sub> is 1-6C alkyl, piperonyl, 3-(benzimidazol-1-yl)propyl, -CZ-NHR<sub>5</sub> or a group (i):



wherein n is 0-3; X is a bond, O, S, NH, CO, CH=CH or a group (ii):



25

R<sub>3</sub> is H, methyl, halo, CN, CF<sub>3</sub> or COR<sub>4</sub>; R<sub>4</sub> is 1-6C alkyl, 3-6C cycloalkyl or phenyl (optionally substituted by methyl or F); Z is O, S, NH, N-methyl or N-CN; and R<sub>5</sub> is 1-8C alkyl, 3-6C cycloalkyl (optionally substituted by

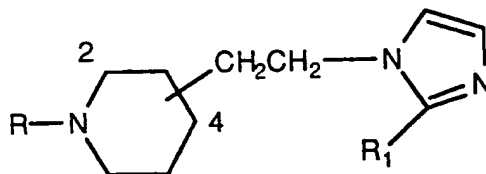
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phenyl), 3-6C cycloalkyl(1-3C)alkyl, phenyl (optionally substituted by methyl, halo or CF<sub>3</sub>), phenyl(1-3C)alkyl, naphthyl, adamantyl or p-toluenesulphonyl. It is disclosed that these compounds are psychotropic agents. It is also disclosed that these compounds

5 antagonize the histamine H<sub>3</sub> receptors and increase the speed of cerebral histamine renewal.

Derwent abstract 90-184730/24 for U.S. 4,925,851 discloses 2- or 4-(2-(1H-imidazol-1-yl)ethyl) piperidine compounds useful as antitumour agents for inhibiting lymphoma, sarcoma, myeloma and leukemia. The

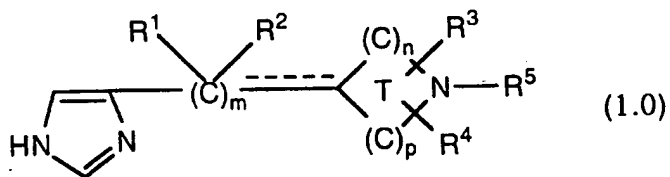
10 compounds have the formula:



wherein R is -CH<sub>2</sub>(CH<sub>2</sub>)<sub>m</sub>-Me, -CO-(CH<sub>2</sub>)<sub>m</sub>-Me or -CO-CMe<sub>2</sub>-R<sub>2</sub>; m is 2-18; R<sub>2</sub> is H or Me; R<sub>1</sub> is -(CH<sub>2</sub>)<sub>n</sub>-R<sub>3</sub>; n is 0-13; R<sub>3</sub> is H, i-Pr or t-Bu; and the floating group is at the 2- or 4- position; with the proviso that (1) the sum of

15 C atoms in R<sub>1</sub> does not exceed 13; and (2) the sum of C atoms in R and R<sub>1</sub> does not exceed 25.

WO 93/12107 published June 24, 1993 discloses a compound of the formula:



20 or a pharmaceutically acceptable salt or solvate thereof, wherein:

- (A) m is an integer selected from the group consisting of: 1 and 2;
- (B) n and p are integers and are each independently selected from the group consisting of: 0, 1, 2, 3, and 4 such that the sum of n and p
- 25 is 4 and T is a 6-membered ring;
- C) R<sup>3</sup> and R<sup>4</sup> are each independently bound to the same or different carbon atom of ring T such that there is only one R<sup>3</sup> group and

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one R<sup>4</sup> group in ring T, and each R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> is independently selected from the group consisting of:

- (1) H;
- (2) C<sub>1</sub> to C<sub>6</sub> alkyl; and
- (3) -(CH<sub>2</sub>)<sub>q</sub>-R<sup>6</sup> wherein q is an integer of: 1 to 7, and R<sup>6</sup> is selected from the group consisting of: phenyl, substituted phenyl, -OR<sup>7</sup>, -C(O)OR<sup>7</sup>, -C(O)R<sup>7</sup>, -OC(O)R<sup>7</sup>, -C(O)NR<sup>7</sup>R<sup>8</sup>, CN and -SR<sup>7</sup> wherein R<sup>7</sup> and R<sup>8</sup> are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C<sub>1</sub> to C<sub>6</sub>)alkyl, halogen, C<sub>1</sub> to C<sub>6</sub> alkyl, -CF<sub>3</sub>, -CN, and -NO<sub>2</sub>, and wherein said substituted phenyl contains from 1 to 3 substituents;
- (D) R<sup>5</sup> is selected from the group consisting of:
  - (1) H;
  - (2) C<sub>1</sub> to C<sub>20</sub> alkyl;
  - (3) C<sub>3</sub> to C<sub>6</sub> cycloalkyl;
  - (4) -C(O)OR<sup>7'</sup>; wherein R<sup>7'</sup> is the same as R<sup>7</sup> defined below except that R<sup>7'</sup> is not H;
  - (5) -C(O)R<sup>7</sup>;
  - (6) -C(O)NR<sup>7</sup>R<sup>8</sup>;
  - (7) allyl;
  - (8) propargyl; and
  - (9) -(CH<sub>2</sub>)<sub>q</sub>-R<sup>6</sup>, wherein q and R<sup>6</sup> are as defined above, and when q is equal to 1, then R<sup>6</sup> is not OH or SH;
- (E) R<sup>7</sup> and R<sup>8</sup> are each independently selected from the group consisting of: H, C<sub>1</sub> to C<sub>6</sub> alkyl, and C<sub>3</sub> to C<sub>6</sub> cycloalkyl;
- (F) the dotted line (-----) represents a double bond that is optionally present when m is 1, and n is not 0, and p is not 0, and when said double bond is present then R<sup>2</sup> is absent; and

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(G) when  $m$  is 2, each  $R^1$  is the same or different substituent for each  $m$ , and each  $R^2$  is the same or different substituent for each  $m$ , and at least two of the substituents  $R^1$  and/or  $R^2$  are H.

These two latter documents claim the use of the compounds for  
5 treatment of allergy and other disorders.

EP 0 428 434 A2 as well as WO 96/29315 and WO 95/06037 describe a wide range of compounds and claim their use as  $H_3$  receptor (ant)agonist. The above documents also include a comprehensive summary of the art dealing with this chemical field.

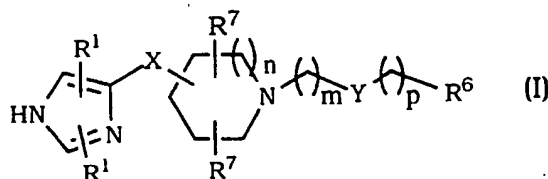
10 US Application Serial. No. 08/689951 filed August 16, 1996 and U.S. Application Serial No. 08/909319 filed August 14, 1997 disclose compositions for the treatment of the symptoms of allergic rhinitis using a combination of at least one histamine  $H_1$  receptor antagonist and at least one histamine  $H_3$  receptor antagonist.

15 In view of the art's interest in compounds which affect the  $H_3$  receptors, novel compounds having antagonist activity on  $H_3$  receptors would be a welcome contribution to the art. This invention provides just such a contribution by providing novel compounds having  $H_3$  antagonist activity.

20

### SUMMARY OF THE INVENTION

This invention relates to compounds of formula I



or pharmaceutically acceptable salts or solvates thereof, wherein:

25 X is a straight chain alkyl group having 1 to 7 carbon atoms or an alkene or alkyne group with 2 to 4 carbon atoms; wherein said alkyl or alkene groups are optionally substituted with up to two (i.e., 1 or 2)  $R^7$  groups;

n is 0, 1 or 2 ,



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m and p are 0 to 4 ;

when m is 0 to 4, Y represents -SO<sub>2</sub>-; -CS-; -CO-; -CONR<sup>5</sup>-;  
-CO(CH<sub>2</sub>)<sub>w</sub>O- (with w being 1 to 4); -COO-; -CON(OR<sup>5</sup>)-; -C(NR<sup>5</sup>)NR<sup>5</sup>-;  
-SO<sub>2</sub>NR<sup>5</sup> - or -CSNR<sup>5</sup>-;

- 5           when m is 2 to 4, Y represents all the groups above when m is 0 to 4 and, in addition, Y represents -CHOR<sup>5</sup>-; -O-; -NR<sup>5</sup>CONR<sup>5</sup>-; -NR<sup>5</sup>CO-;  
-NR<sup>5</sup>-; -OCONR<sup>5</sup>-; -NR<sup>5</sup>C(NR<sup>5</sup>)NR<sup>5</sup>-; -NR<sup>5</sup>CSNR<sup>5</sup>-; -NR<sup>5</sup>CS- or -NR<sup>5</sup>SO<sub>2</sub>-;  
-NR<sup>5</sup>C(O)O-; or -CSNR<sup>5</sup>-;

each R<sup>5</sup> independently represents hydrogen, alkyl or benzyl;

- 10           R<sup>6</sup> represents aryl, heteroaryl, or a 3- to 7- membered heterocyclic group having one to three heteroatoms in the ring, wherein the heteroatoms are selected from N, S and O, and wherein said R<sup>6</sup> group is optionally substituted by one to three substituents as defined below;

- when Y is -SO<sub>2</sub> -, then R<sup>6</sup>, in addition to the above groups, also  
15           represents alkyl having 1 to 7 carbon atoms or a group -NR<sup>10</sup>R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> are independently selected from H, alkyl or trihalomethyl;

each R<sup>1</sup> is independently hydrogen, alkyl or trihalomethyl;

- each R<sup>7</sup> is independently selected from hydrogen, alkyl,  
trihalomethyl, phenyl or benzyl, , wherein said phenyl and benzyl are  
20           optionally substituted by one to three substituents independently selected from of alkyl, halogen, trihalomethyl, CN, NO<sub>2</sub>, OR<sup>10</sup> or NR<sup>10</sup>R<sup>11</sup>, wherein R<sup>10</sup> and R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> as above defined.

- This invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount  
25           of a compound (or a salt or solvate thereof) of Formula I.

- This invention further provides a method of treating allergy, (for example asthma), inflammation, cardiovascular disease, hypotension, raised intraocular pressure (such as glaucoma)--i.e., a method of lowering intraocular pressure, sleeping disorders (e.g., hypersomnia, somnolence,  
30           narcolepsy and sleeplessness, such as insomnia), diseases of the GI tract, states of hyper and hypo motility and acidic secretion of the gastro-intestinal tract, disturbances of the central nervous system, hypo and

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hyperactivity of the central nervous system (for example, agitation and depression) and other CNS disorders (such as Alzheimer's, schizophrenia, obesity and migraine) comprising administering an effective amount of a compound, or a salt or solvate thereof, of Formula I  
5 to a patient in need of such treatment.

This invention further provides a method for treating upper airway allergic responses by comprising administering an effective amount of a compound, or a salt or solvate thereof, of Formula I in combination or admixture with a suitable H<sub>1</sub> receptor antagonist.

10

#### DETAILED DESCRIPTION OF THE INVENTION

As used herein the following terms have the following meanings unless indicated otherwise:

alkyl - represents a straight or branched, saturated hydrocarbon  
15 chain having from 1 to 6 carbon atoms;

lower alkyl (including the alkyl portions of lower alkoxy) – represents a straight or branched, saturated hydrocarbon chain having from 1 to 6 carbon atoms, preferably from 1 to 4;

cycloalkyl - represents a saturated carbocyclic ring having from  
20 3 to 6 carbon atoms, optionally substituted by 1 to 3 groups independently selected from the group consisting of lower alkyl, trihalomethyl and NR<sup>10</sup>R<sup>11</sup>, wherein R<sup>10</sup> and R<sup>11</sup> as defined above;

halogen (halo) - represents fluoro, chloro, bromo or iodo;

aryl – represents a carbocyclic group having from 6 to 14 carbon  
25 atoms and having at least one benzenoid ring, with all available substitutable aromatic carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted with 1 to 3 groups, each independently selected from halo, alkyl, hydroxy, phenoxy, amino, loweralkylamino,  
30 diloweralkylamino, (e.g., NR<sup>10</sup>R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> are independently selected from hydrogen, lower alkyl or trihalomethyl), loweralkoxy, polyhaloloweralkoxy, (e.g., OR<sup>10</sup> wherein R<sup>10</sup> is as above defined) polyhaloloweralkyl (e.g., trihalomethyl), CN, or NO<sub>2</sub>; preferred aryl groups

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include 1-naphthyl, 2-naphthyl and indanyl, and especially phenyl and substituted phenyl;

heterocyclic – represents saturated and unsaturated non-aromatic cyclic organic groups having at least one O, S and/or N atom interrupting a carbocyclic ring structure that consists of one ring or two fused rings, wherein each ring is 3 to 7 membered (e.g., 5-, 6- or 7-membered), which ring structure has from 2 to 8, preferably from 3 to 6 carbon atoms; e.g., 2- or 3-pyrrolidinyl, 2-, 3- or 4-piperidinyl, 2- or 3-piperazinyl, 2- or 3-morpholinyl, or 2- or 3-thiomorpholinyl; said heterocyclic group being optionally substituted by 1 to 3 groups independently selected from alkyl, trihalomethyl and  $\text{NR}^{10}\text{R}^{11}$ , wherein  $\text{R}^{10}$  and  $\text{R}^{11}$  are independently selected from hydrogen, alkyl or trihalomethyl, said substituents being bound to carbon atoms (substitutable carbon atoms) in the ring such that the total number of substituents in the ring is 1 to 3; and wherein said heterocyclic ring contains nitrogen atoms, said nitrogen atoms (i.e., the substitutable nitrogen atoms) being optionally substituted with lower alkyl (e.g., methyl), e.g., N-methylpyrrolidinyl;

heteroaryl – represents a cyclic organic group having at least one O, S and/or N atom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic group having from 2 to 14, preferably 4 or 5 carbon atoms, e.g., 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2- or 4-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, or 3- or 4-pyridazinyl, etc.; preferred heteroaryl groups are 2-, 3- and 4-pyridyl; said heteroaryl groups being optionally substituted with 1 to 3 groups, each optional substituent being independently selected from alkyl, halogen, trihalomethyl, CN,  $\text{NO}_2$ ,  $\text{OR}^{10}$  or  $\text{NR}^{10}\text{R}^{11}$ , wherein  $\text{R}^{10}$  and  $\text{R}^{11}$  are independently selected from hydrogen, alkyl or trihalomethyl, said substituents being bound to carbon atoms (substitutable carbon atoms) in the ring such that the total number of substituents in the ring is 1 to 3;

DMF - stands for N, N,-dimethylformamide;

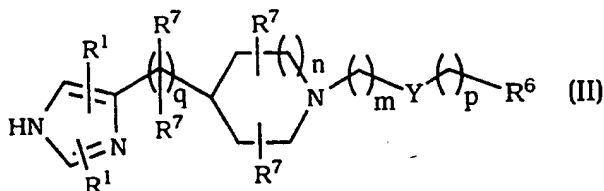
SEM - stands for 2-(trimethylsilyl)ethoxymethyl;

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- THF - stands for tetrahydrofuran;  
 DMAP - stands for dimethylaminopyridine;  
 DIPA - stands for diisopropylamine;  
 DMSO - stands for dimethyl sulfoxide;  
 5 DBU - stands for diazabicycloundecene;  
 DBN - stands for diazabicyclononane;  
 LAH - stands for lithium aluminum hydride;  
 FAB - stands for fast atom bombardment;  
 10 CI - stands for chemical ionization;  
 EI - stands for electron impact;  
 HOBT - stands for 1-hydroxybenzotriazole;  
 EDCI - stands for 1-(3-dimethylaminopropyl)-3-ethylcarbo-  
 diimide hydrochloride;  
 LC/MS - stands for liquid chromatography/mass spectrometry;  
 15 TFA - stands for trifluoroacetic acid;  
 Tr - stands for trityl; and  
 LRMS - stands for low resolution mass spectrometry.

Also, unless stated otherwise, the substituents for the various  
 embodiments described below are as defined for Formula I.

- 20 Preferred compounds are represented by of formula II



- wherein q is 1 to 7, m is 0 to 4, n is 0 or 1, p is 0 to 4, Y is selected from  
 -SO<sub>2</sub> -, -SO<sub>2</sub>NH-, -CONH-, -CO-, -C(NH)NH-, or -CO(CH<sub>2</sub>)<sub>w</sub> O-, or, when m  
 is 2 to 4, Y, in addition to the groups above, also represents -NHCONH-,  
 25 -O- or -NHC(NH)NH-; and w, R<sup>1</sup>, R<sup>6</sup>, and R<sup>7</sup> are as defined above.

Preferably R<sup>6</sup> is phenyl or substituted phenyl.

- Most preferred are compounds of formula II wherein (1) q is 1 to 4; (2) n is  
 0 or 1; (3) m is 0 to 4 (more preferably, 0 to 3, and even more preferably 0  
 to 2); (4) p is 0 to 2; (5) Y is -CONH-, -CO-, -SO<sub>2</sub>-, -CO(CH<sub>2</sub>)<sub>2</sub>O- or -O-  
 30 (when m is greater than or equal to 2, i.e., Y can also be -O- when m is 2-

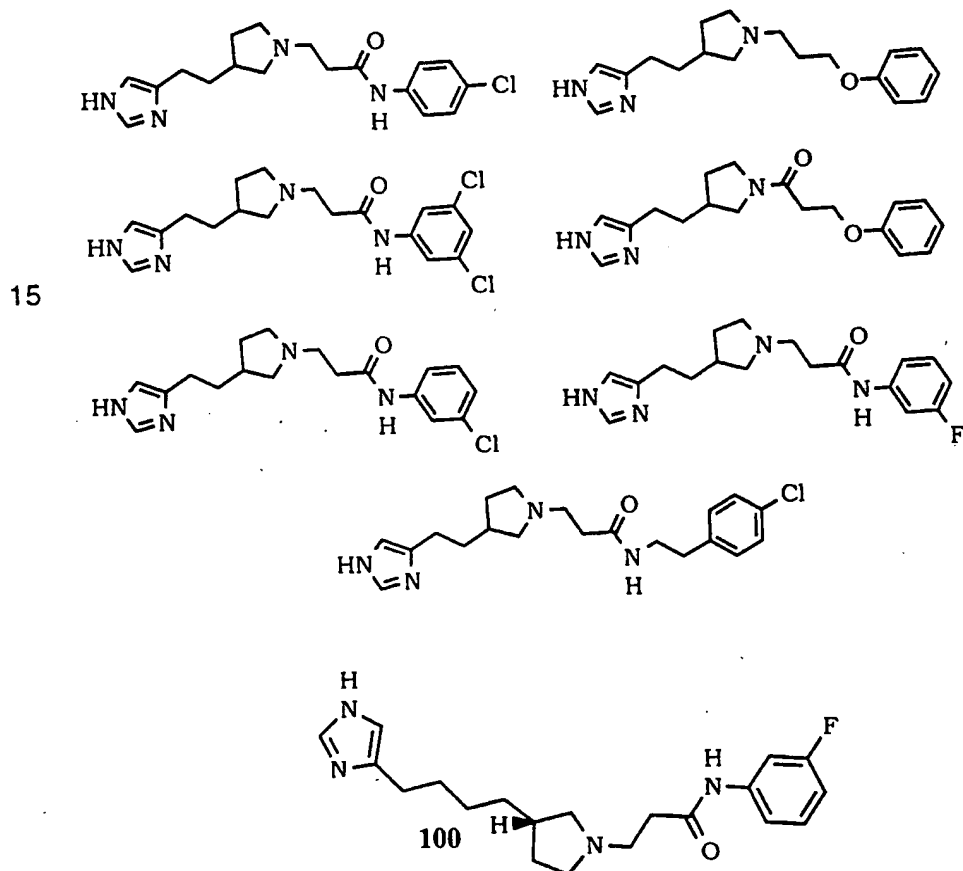
- 10 -

4); (6) R<sup>6</sup> is phenyl, wherein said phenyl is optionally substituted by one, two or three substituents independently selected from halogen, preferably fluorine or chlorine, CF<sub>3</sub>, C<sub>1</sub> to C<sub>4</sub> alkoxy, OCF<sub>3</sub>, NO<sub>2</sub>, or NR<sup>10</sup>R<sup>11</sup> with R<sup>10</sup> and R<sup>11</sup> being as defined above.

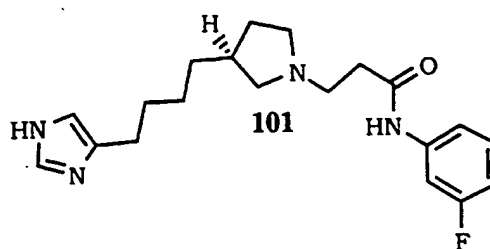
5 For the compounds of formula II, R<sup>1</sup> and R<sup>7</sup> are preferably hydrogen.

For the compounds of formula II, preferably when R<sup>6</sup> is mono-substituted phenyl said substituent is in the 3- or 4-position and said substituent is selected from fluorine, chlorine, methoxy or trifluoromethoxy, and when R<sup>6</sup> is disubstituted phenyl said substituents are in the 3,5-positions and said substituents are the same and are selected from fluorine, chlorine, methoxy or trifluoromethoxy.

Compounds of this invention include, but are not limited to

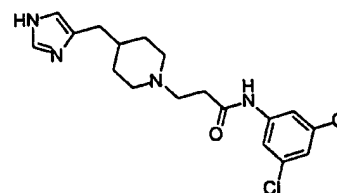
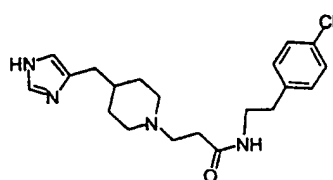
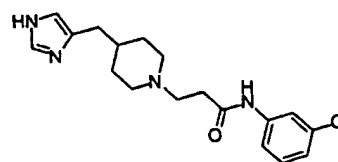
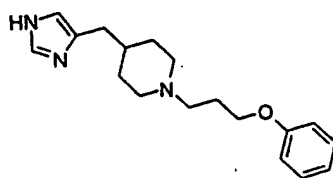


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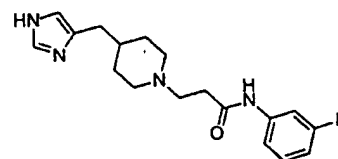
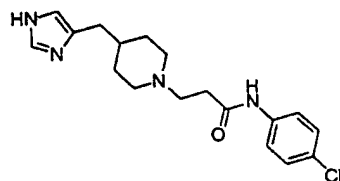


and

Compounds of this invention also include, but are not limited to



5



and

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention  
 10 contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

10

The compounds of Formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as  
 15 water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

15

Certain basic compounds of the invention also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the nitrogen atoms may form salts with acids. Examples of suitable acids

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for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate.

10       The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

15       All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

20       Numerous chemical substances are known to have histamine H<sub>1</sub> receptor antagonist activity. Many useful compounds can be classified as ethanolamines, ethylenediamines, alkylamines, phenothiazines or piperidines. Representative H<sub>1</sub> receptor antagonists include, without limitation: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine (also known as SCH-34117), diphenhydramine, doxylamine, dimethindene, ebastine, 25       epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine and triprolidine.

30       Other compounds can readily be evaluated to determine activity at H<sub>1</sub> receptors by known methods, including specific blockade of the contractile response to histamine of isolated guinea pig ileum. See for example, WO98/06394 published February 19, 1998.

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For example, the H<sub>3</sub> antagonists of this invention can be combined with an H<sub>1</sub> antagonist selected from astemizole, azatadine, azelastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, carebastine, descarboethoxyloratadine (also known as SCH-34117), diphen-  
5 hydramine, doxylamine, ebastine, fexofenadine, loratadine, levocabastine, mizolastine, norastemizole, or terfenadine.

Also, for example, the H<sub>3</sub> antagonists of this invention can be combined with an H<sub>1</sub> antagonist selected from, azatadine, bromphen-  
iramine, cetirizine, chlorpheniramine, carebastine, descarboethoxy-  
10 loratadine (also known as SCH-34117), diphenhydramine, ebastine, fexofenadine, loratadine, or norastemizole.

Representative combinations include: the H<sub>3</sub> antagonists of this invention with loratadine, H<sub>3</sub> antagonists of this invention with descarboethoxyloratadine, H<sub>3</sub> antagonists of this invention with  
15 fexofenadine, and H<sub>3</sub> antagonists of this invention with cetirizine.

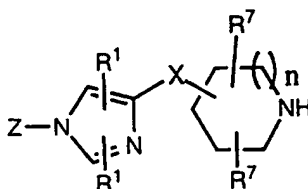
Those skilled in the art will know that the term "upper airway" means the upper respiratory system--i.e., the nose, throat, and associated structures.

The compounds of this invention may be prepared according to  
20 suitable processes known in the art for making similar compounds, e.g. processes described in the literature referred to above.

The following processes may be employed to produce compounds of Formula I. Unless stated otherwise, reactions are conducted at an appropriate temperature which allows the reaction to proceed at a  
25 reasonable rate to completion.

#### GENERAL PREPARATION SCHEMES.

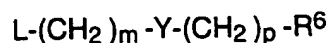
In general the compounds of this invention are prepared by first providing starting compounds of the general formula





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which then in a further step are reacted with a compound of the general formula



followed by elimination of the protecting group Z to yield a compound of

5 formula I.

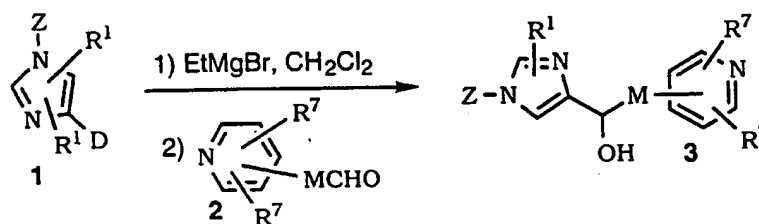
In the above formulae  $R^1$ ,  $R^6$ ,  $R^7$ , X, Y, m, n and p are as defined for formula I above. L represents a leaving group such as Cl, Br, I, and activated versions of OH such as  $OSO_2CF_3$  generated independently or in situ.

10 The following reaction schemes illustrate the various steps of the processes used.

#### PREPARATION OF PIPERIDINES ( $n = 1$ )

##### Reaction Scheme 1 - Compounds wherein X is $-(CH_2)_{1-7}$

##### Step 1



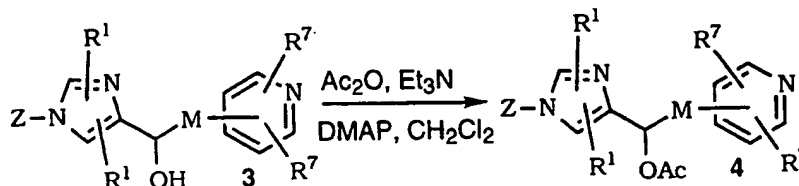
0 °C - RT

15

Compound 1, wherein (1) D is halogen, preferably iodide, (2) Z represents a protecting group such as triphenylmethyl, 2-(trimethylsilyl)-ethoxymethyl and the like, and (3)  $R^1$  can be either hydrogen, alkyl or trihalomethyl, is dissolved in a suitable solvent, such as methylene chloride, and treated with a Grignard reagent, such as ethylmagnesium bromide. Subsequent addition of an appropriate aldehyde 2 ( $M = (CH_2)_0-$  6) produces compound 3.

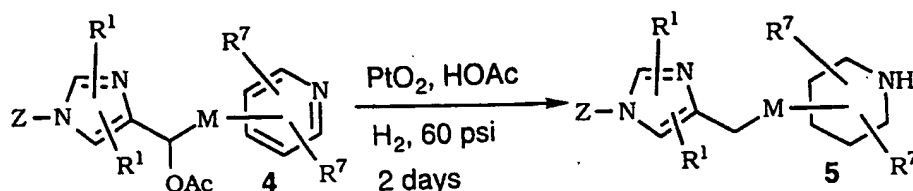
20

##### Step 2

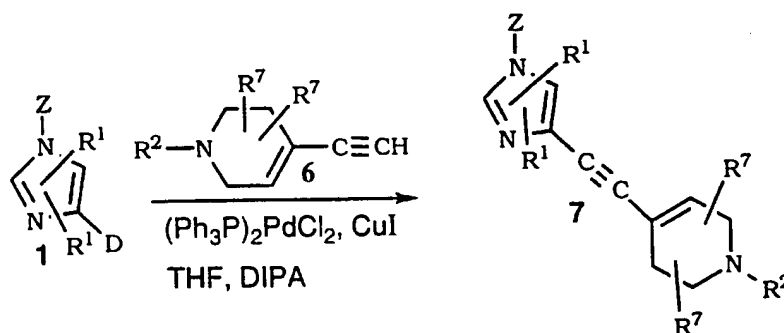


- 15 -

In step 2, compound 3 is dissolved in an organic solvent, such as methylene chloride, and treated with a tertiary amine base, such as triethylamine, and an acylation catalyst, such as dimethylaminopyridine. Subsequent treatment with acetic anhydride provides the compound of formula 4.

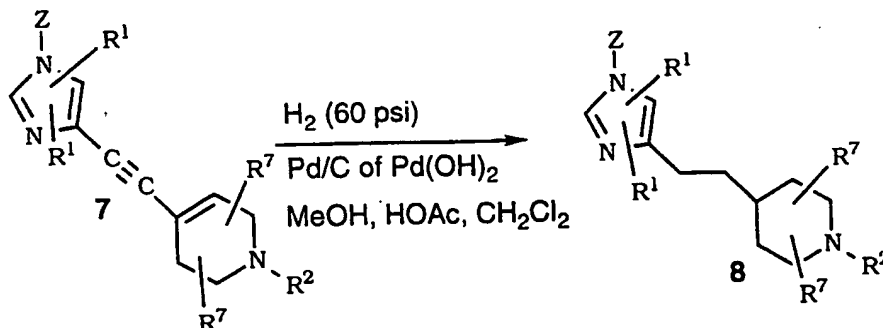
Step 3

In step 3, compound 4 is dissolved in a suitable organic acid, such as acetic acid, and hydrogenated under pressure (16-60 psi) in the presence of an appropriate catalyst, such as platinum oxide, to provide compound 5.

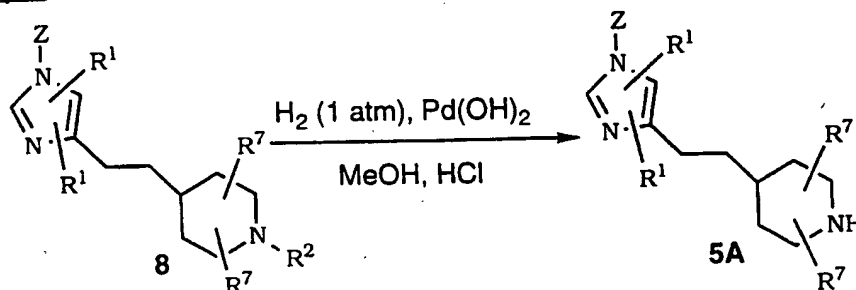
Reaction Scheme 2 - Compounds wherein X is -(CH<sub>2</sub>)<sub>2</sub>-Step 1

In Step 1, compound 1, wherein (1) D = halogen, preferably iodide, (2) Z represents a protecting group such as triphenylmethyl, 2-(trimethylsilyl)ethoxymethyl and the like, and (3) R<sup>2</sup> represents benzyl or substituted benzyl, is dissolved in a suitable solvent or a mixture of solvents selected from ethereal and dialkylamine solvents. A tetrahydrofuran/diisopropylamine mixture is preferred. Addition of a compound of structure 6 followed by addition of a suitable catalyst, such as bistrisphenylphosphine-palladium dichloride and copper iodide, and stirring at temperatures from 21-60 °C provides compound 7.

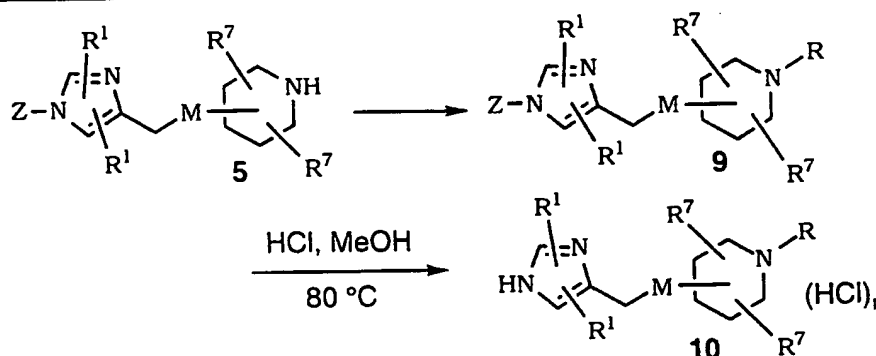
- 16 -

Step 2

In Step 2, compound 7 is dissolved in a suitable organic solvent or mixtures thereof (examples of solvents include methylene chloride, methanol, and acetic acid) and hydrogenated with a catalyst, such as palladium or palladium hydroxide, at pressures ranging from 16-60 psi to provide compound 8.

Step 3

In Step 3, compound 8 is dissolved in a suitable alcohol, such as methanol, and treated with a few drops of hydrochloric acid (1M) and hydrogenated with a suitable catalyst, such as palladium or palladium hydroxide, at pressures ranging from 16-60 psi to provide compound 5A.

Reaction Scheme 3 - Preparation of Compound 10

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(wherein R is the group  $-(CH_2)_m-Y-(CH_2)_p-R^6$ ).

Those skilled in the art will appreciate that the number of HCl molecules (r) is based on the number of basic groups present in compound 10.

- 5 Compound 5 is reacted with  $L-(CH_2)_m-Y-(CH_2)_p-R^6$  to produce compound 9. L is a leaving group, such as Cl, Br, I and activated versions of OH, such as  $OSO_2CF_3$  generated independently or in situ. When Y is  $-C(O)NH-$ ,  $-OCO$  and  $-SO_2-$ , and m is 2, then compound 5 is reacted with reactants such as  $(CH_2=CH)C(O)O(CH_2)_pR^6$ ,  
 10  $(CH_2=CH)C(O)NR^5(CH_2)_pR^6$ , and  $(CH_2=CH)SO_2(CH_2)_pR^6$ .

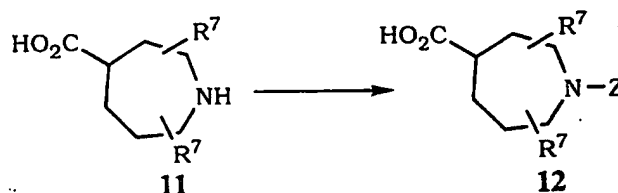
- The reactions are conducted in suitable solvents, such as ether, tetrahydrofuran, dioxane, dimethylsulfoxide, dimethylformamide, water, methylene chloride, and toluene, with or without the presence of a suitable bases, such as triethylamine, lithium diisopropylamide or sodium hydride,  
 15 at temperatures ranging from  $-78^\circ$  to  $200^\circ C$ .

When Z is triphenylmethyl, compound 9 is deprotected by treatment with dilute aqueous acid, such as HCl or HBr, at a temperature of about  $25^\circ$  to  $100^\circ C$  to produce compound 10. Other protecting groups are removed by methods well known in the art.

20 PREPARATION OF COMPOUNDS HAVING A 7-MEMBERED HETERO-CYCLIC RING

Reaction Scheme 4 - Compounds wherein X is  $-CH_2-$

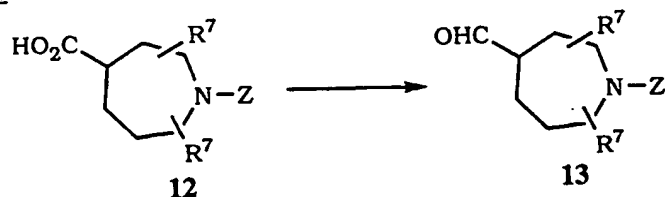
Step 1



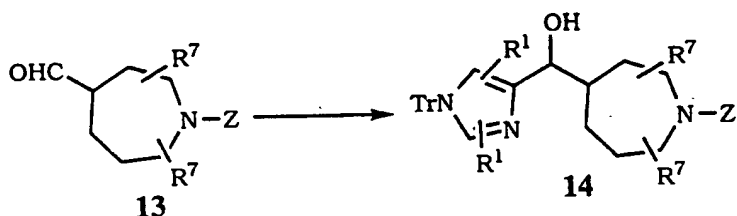
- 25 In Step 1, compound 11 (prepared in an analogous manner to the procedures outlined in *European J. Med Chem.* **1979**, *14*, 157-164 and *Tetrahedron Letts.* **1990**, *31*, 933-936) is reacted with a compound ZCl in a suitable organic solvent at a temperature of from  $0^\circ$  to about  $50^\circ C$  in the presence of an organic base to produce compound 12. Z represents a  
 30 protecting group, preferably carbobenzyloxy. Suitable solvents include

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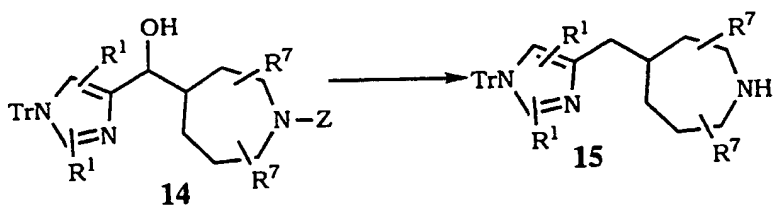
THF, ether, dioxane or the like. Suitable bases include triethylamine and the like.

Step 2

- 5 In Step 2, compound **12** is reduced to the aldehyde **13** using a suitable reducing agent, such as  $\text{BH}_3 \cdot \text{SMe}_2$  or the like, in a suitable organic solvent, such as THF, ether, dioxane or the like, at a temperature of 0° to 100°C.

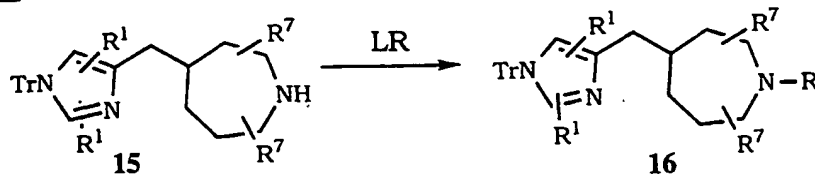
Step 3

- 10 In Step 3, compound **13** is reacted with the Grignard reagent formed from imidazole in the same manner as described for Step 1 of Reaction Scheme 1 to give the alcohol **14**.

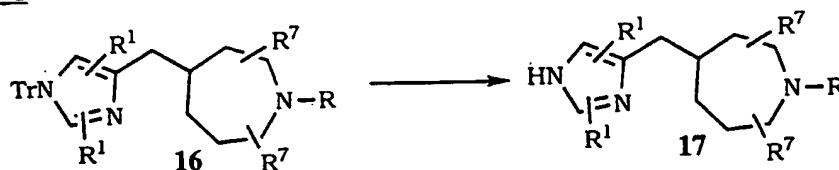
Step 4

- 15 In Step 4, compound **14** is reduced to compound **15** in a suitable polar organic solvent using  $\text{H}_2$  in the presence of a metal catalyst and a trace of acid at a temperature of from 25° to 75°C. Suitable solvents include MeOH, EtOH and i-PrOH, with EtOH being preferred, and catalysts  
 20 can include Pd/C or  $\text{PtO}_2$  or the like.

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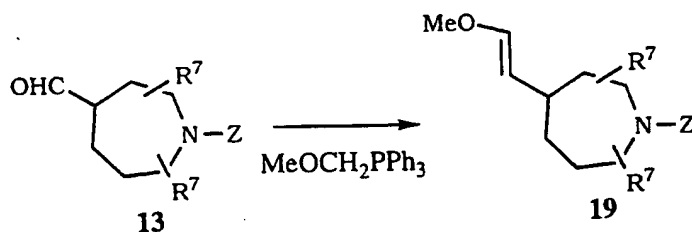
Step 5

- In Step 5, compound 15 is reacted with LR in a suitable solvent such as THF, ether, or the like in the presence of a suitable tertiary amine base such as triethylamine at a temperature from 0°C to 100°C, preferably 25°C, to produce compound 16. R is  $-(CH_2)_m-Y-(CH_2)_p-R^6$  and L is a leaving group as defined in Reaction Scheme 3 above.

Step 6

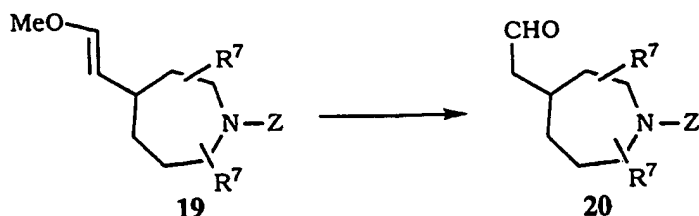
- Step 6 is performed in a similar manner to the deprotection step in Reaction Scheme 3 above to give compound 17.

Reaction Scheme 5 - X is  $-(CH_2)_2$ :-

Step 1

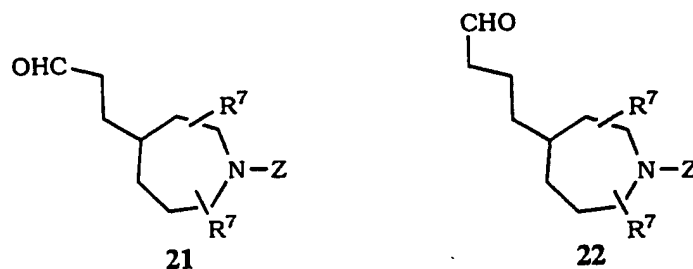
- In Step 1, aldehyde 13 is reacted with the Wittig reagent in a suitable ethereal solvent in the presence of a strong base at a temperature from -25° to 80°C to give compound 19. Suitable solvents include THF, ether, dioxane or the like. Strong bases can include lithium or potassium diisopropylamide, and lithium, sodium or potassium bis(trimethylsilyl)-amide or the like. Other suitable bases can include NaH or KH in a suitable polar aprotic solvent, such as DMSO.

- 20 -

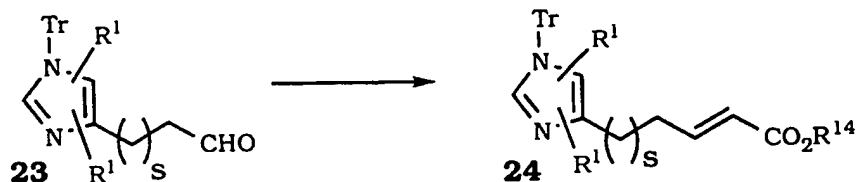
Step 2

In Step 2, the enol ether **19** is hydrolyzed to the aldehyde **20** by treatment with a dilute mineral acid, such as HCl or HBr, at a temperature from 0° to about 80°C. Aldehyde **20** can then be converted to the desired targets in a manner similar to that described in Reaction Scheme 4, Steps 3 to 6.

Reaction Scheme 6 - X is  $-(CH_2)_3-$  to  $-(CH_2)_7-$



Aldehyde **20** can be converted to aldehyde **21** in a similar manner to that described in Reaction Scheme 5. Compound **21** can then be converted to the desired targets in a manner similar to that described in Reaction Scheme 4, Steps 3 to 6. A similar sequence can be applied to compound **22** and to higher homologs.

PREPARATION OF PYRROLIDINES (n = 0)Reaction Scheme 7Step 1

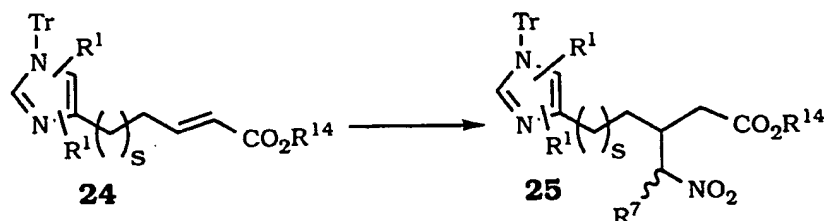
wherein  $s$  is 0 to 5, and  $R^{14}$  represents lower alkyl (e.g., methyl or ethyl).

In Step 1, a suitable Horner-Emmons reagent such as trimethyl- or triethyl phosphonoacetate is treated with a strong base, such as NaH, KH,

- 21 -

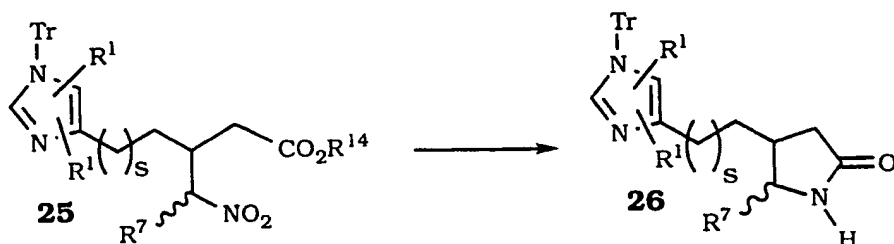
lithium diisopropylamide or the like, in a suitable ethereal solvent such as THF, ether, dioxane or the like. The phosphonate carbanion is then reacted with the aldehyde **23** for 30 min. to 24 h at a temperature suitable to complete the reaction and give ester **24**.

### 5 Step 2



In Step 2, ester **24** is reacted with a substituted or unsubstituted nitroalkane, such as nitromethane or nitroethane, in a polar aprotic solvent, such as acetonitrile, THF or the like, preferably acetonitrile, in the presence of an amine base, such as DBU, DBN, triethylamine or the like, preferably DBU, at a temperature from  $0^\circ\text{C}$  to  $80^\circ\text{C}$ , preferably  $25^\circ\text{C}$ , for 24h to yield nitro ester **25**.

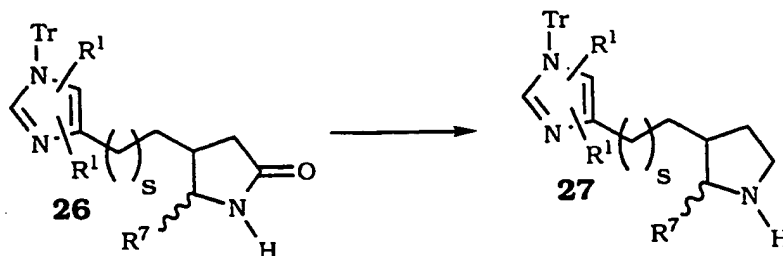
### Step 3



In Step 3, the nitro group of nitro ester **25** is reduced to the amine using hydrogen and a suitable metal catalyst, such as  $\text{Pd/C}$ ,  $\text{Ra-Ni}$  or the like, in a suitable protic solvent, such as methanol, ethanol or the like, at a temperature of from  $25^\circ$  to  $80^\circ\text{C}$ . The resulting amino ester is cyclized to the lactam by heating in a suitable protic solvent, such as methanol or ethanol, at a temperature of up to  $80^\circ\text{C}$  in the presence of a small amount of a base such as potassium carbonate or the like to give compound **26**.



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Step 4

In Step 4, compound 26 is reacted with a suitable reducing agent, such as LAH,  $\text{BH}_3$ , or the like, preferably LAH, in a suitable solvent, such as THF, ether, dioxane or the like, at a temperature ranging from  $0^\circ$  to  $80^\circ\text{C}$ , preferably  $60^\circ\text{C}$ , for a time ranging from 30 min. to 24h, preferably 3h to give compound 27.

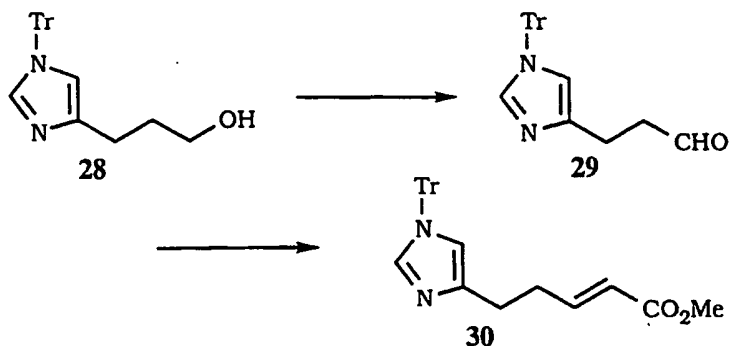
Compound 27 is then reacted with a compound of the formula  $\text{L}-(\text{CH}_2)_m-\text{Y}-(\text{CH}_2)_p-\text{R}^6$  followed by deprotection in a manner similar to the procedure outlined for Reaction 3 above.

The starting compounds of formula 23 are either known compounds or may be obtained according to procedures well known in the art, for example by following the preparations in the steps outlined for compounds 13, 20, and 22 above.

A person skilled in the art will easily see that several variations of the above processes are possible. For example, the substituents  $\text{R}^1$  and  $\text{R}^7$  may be present in the starting materials or may be introduced at any convenient stage of the process.

The following examples are intended to illustrate, but not to limit, the present invention.

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EXAMPLE 1Step A

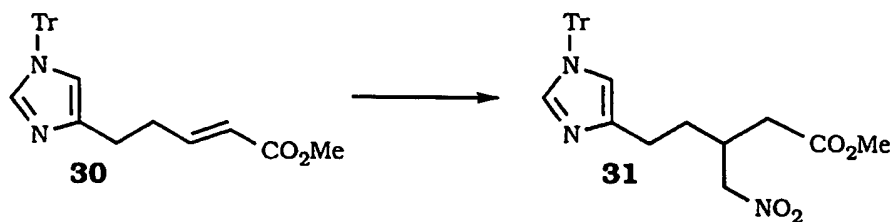
To a flask containing oxalyl chloride (13.8 g, 9.5 ml, 109 mmols) in  
5 methylene chloride (300 ml) at  $-78^{\circ}\text{C}$  was added DMSO (19.9 g, 255  
mmols) dropwise. When gas evolution stopped, the mixture was stirred for  
8 min., and a solution of the alcohol 28 (10.0 g, 27.2 mmols) in methylene  
chloride (50 ml) was added. The reaction was maintained at  $-78^{\circ}\text{C}$  for 50  
min., triethylamine (45 ml, 255 mmol) was added, and the reaction  
10 allowed to warm to room temperature over 45 min. The contents were  
diluted with  $\text{NH}_4\text{Cl}$  solution and extracted with methylene chloride. The  
combined organics were washed with brine, dried over  $\text{MgSO}_4$ , filtered  
and concentrated. The crude product was chromatographed over silica  
gel (10 to 30% acetone in methylene chloride) to give the product 29 as a  
15 faint yellow oil (7.7 g, 77%): LRMS (CI,  $\text{M}+\text{H}$ ) = 367.

To a flask containing NaH (95%, 2.0 g, 79 mmol), was added dry  
THF (600 ml) under a nitrogen atmosphere. To this mixture was added  
trimethylphosphonoacetate (14.0 g, 77.5 mmols) dropwise via syringe.  
Gas evolution was observed and a viscous white mixture resulted. The  
20 mixture was warmed to  $35^{\circ}\text{C}$  for 30 min. and then allowed to cool back to  
room temperature. The aldehyde 29 (14.5 g, 39.6 mmols) in dry THF (200  
ml) was added via syringe to the reaction mixture. TLC (40% EtOAc-Hex)  
indicated the reaction to be complete after stirring for 45 min. at r.t. The  
contents were diluted with water, and the aqueous portion was extracted  
25 with EtOAc. The combined organics were washed with brine, dried over  
 $\text{MgSO}_4$ , filtered and concentrated to give a solid which was recrystallized  
from  $\text{Et}_2\text{O}$ -hexane (1:2 v/v) to give 5.9 g of pure material. The mother

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liquors were chromatographed on silica gel (40% EtOAc-hexane → 60% EtOAc) to afford another 7.7 g of material, 81% combined yield. LRMS (CI, M+H) = 423. Analytical CHN for (C<sub>28</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>): C, 79.25; H, 6.22; N, 6.60: Found C, 79.11; H, 6.39; N, 6.66. mp = 129-130.5°C

### 5 Step B



To a CH<sub>3</sub>CN solution (300 ml) of **30** (11.0 g, 26.1 mmols) was added CH<sub>3</sub>NO<sub>2</sub> (29.3 g, 26 ml, 480 mmols) followed by DBU (5.1 g, 5.0 ml, 33.4 mmols). The reaction mixture was stirred under a nitrogen atmosphere for 18 h, at which time no starting material was observed by TLC (40% EtOAc-Hex). The solvents were evaporated under reduced pressure, and the residue was chromatographed directly on silica gel (50% EtOAc-Hex → 70% EtOAc) affording 13.1 g (>100% crude yield) of the product as a colorless oil. LRMS (CI, M+H) = 484. Analytical CHN for (C<sub>29</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>): C, 72.03; H, 6.04; N, 8.69: Found C, 72.06; H, 6.34; N, 8.66. mp = 97.5-99.5°C.

### Step C



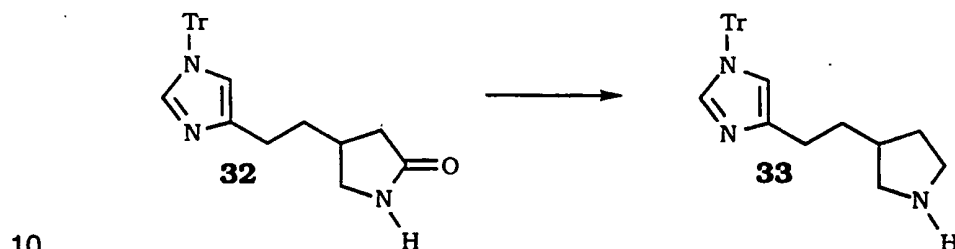
Compound **31** (2 x 5 g, 20.7 mmols) was dissolved in a solution of absolute EtOH-THF (60-20, v/v). Ra-Ni (~2 x 5 g) was added, and the Parr vessel was pressurized to 50 psi with hydrogen. After shaking for 4-6 h, TLC indicated the reduction to the amino-ester was complete (10% MeOH-EtOAc). The catalyst was removed by filtering through celite. Evaporation under reduced pressure afforded the amino-ester intermediate which was subsequently cyclized to the lactam by refluxing in

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MeOH with a small amount of  $K_2CO_3$  for 3 h. Removal of the  $K_2CO_3$  by filtration and evaporation of the solvent afforded an oil which was chromatographed on silica gel (10% MeOH- $CH_2Cl_2$   $\rightarrow$  10% MeOH + 2%  $NH_4OH$ ) to give the product as an off white amorphous solid, 8.1 g (92%).

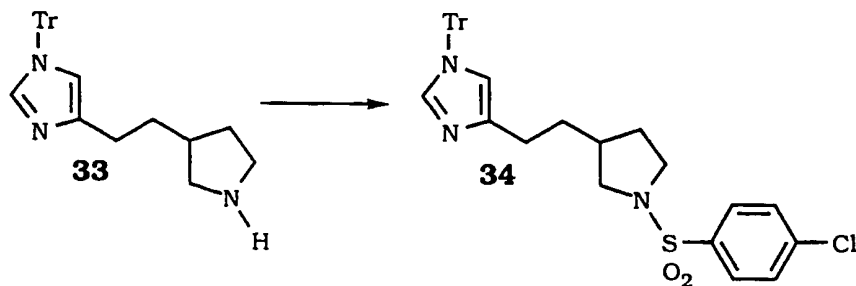
- 5 LRMS (CI, M+H) = 422. Analytical CHN for ( $C_{28}H_{27}N_3O \times 1.5$  mol  $H_2O$ ): C, 74.91; H, 6.57; N, 9.36: Found C, 74.76; H, 6.17; N, 9.14. MP = 171-173.5 °C.

Step D



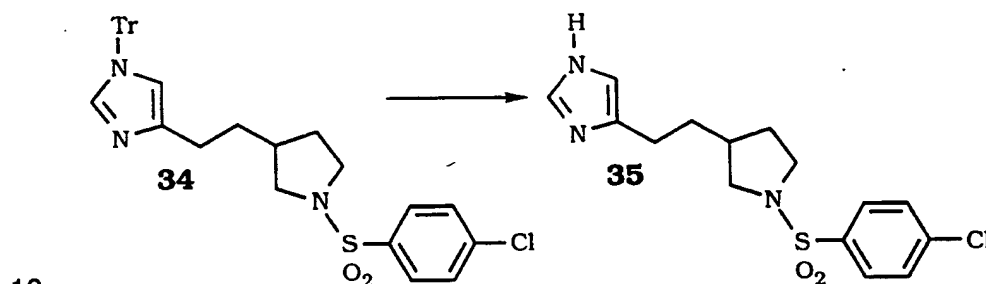
- To a flask containing a THF (12 ml) solution of LAH (180 mg, 4.80 mmols, 10 equiv.) was added a THF solution of **32** at room temperature. The mixture was heated to 60°C for 3 h, then allowed to cool to r.t. The reaction was quenched by the addition of solid  $Na_2SO_4 \times 10H_2O$ . After 20 min. 5% NaOH (~ 1 ml) was added causing the viscous gray mixture to become colorless and homogeneous. After another 20 min. the mixture was filtered through celite and the filter cake was washed well with THF and MeOH. The effluent was concentrated under reduced pressure and then chromatographed on silica gel (10% MeOH- $CH_2Cl_2$   $\rightarrow$  10% MeOH + 2%  $NH_4OH$ ) to afford 168 mg (73%) of the product **33** as hygroscopic foam. LRMS (CI, M+H) = 408.

Step E



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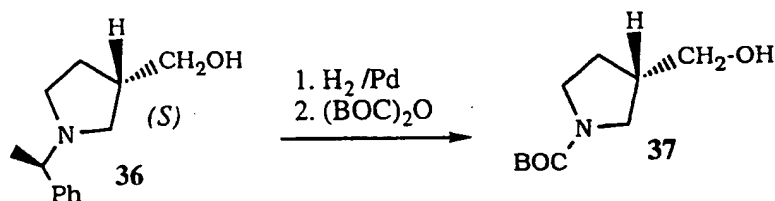
To a  $\text{CH}_2\text{Cl}_2$  solution (6 ml) of (+/-)**33** (315 mg, 0.774 mmols) was added  $\text{Et}_3\text{N}$  (2 ml, 14.4 mmols) followed by p-chlorosulfonyl chloride (215 mg, 1.09 mmols) at r.t. The mixture was stirred under a nitrogen atmosphere for 21 h, then evaporated to 1/2 volume and chromatographed on silica gel (1%  $\text{MeOH}-\text{CH}_2\text{Cl}_2 \rightarrow 3\% \text{MeOH}$ ) which afforded an amorphous white solid. Trituration with hexane-acetone followed by evaporation yielded a fluffy white foam. LRMS ( $\text{Cl}, \text{M}+\text{H}$ ) = 582.

**Step F**

Standard HCl deprotection of **34** provides the hydrochloride salt of **35** as a light tan solid. LRMS ( $\text{Cl}, \text{M}+\text{H}$ ) = 340.

**Example 1A: Chiral Synthesis**

15 **Step A**

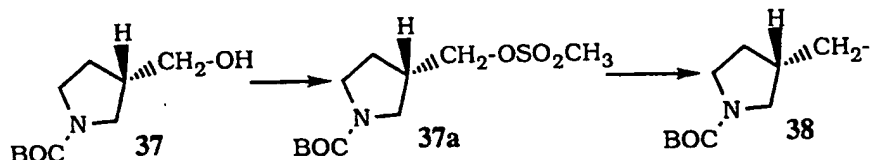


A solution of **36** (2.0g) in ethanol (20 ml) and 10% palladium-on-carbon (0.3g) is hydrogenated in a Parr shaker at 60 psi for 24 hr. The catalyst is then filtered and the filtrate is evaporated under reduced pressure. The residual oil is dissolved in dichloromethane (20 ml). Di-*tert* butyldicarbonate (2g) is added to the solution followed by 4-dimethylaminopyridine (0.05g). The reaction mixture is stirred at 70°C for 1 hour and is then evaporated under reduced pressure. The product is then flash chromatographed on silica gel (50 ml). Elution with 8% methanol-

- 27 -

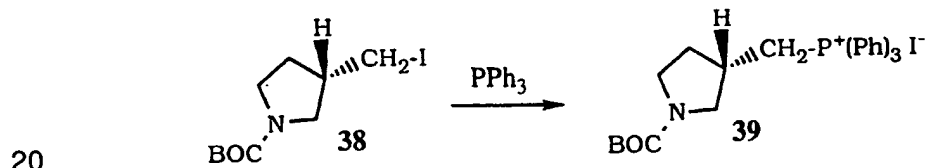
dichloromethane afforded after evaporation under reduced pressure the title compound **37** as a colorless oil (1.1g), MS (CI) m/e=146 (M-56).

### Step B



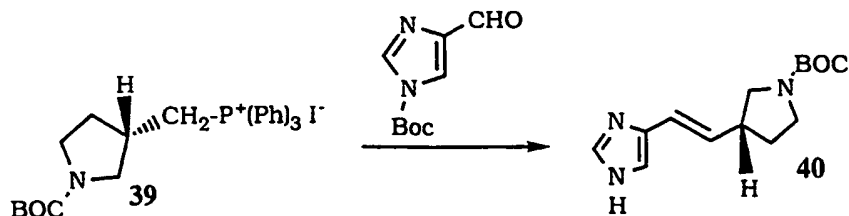
- 5 A solution of **37** (1.1g) and triethylamine (0.84 ml) in dichloromethane is cooled in an ice-bath and stirred while adding dropwise a solution of mesyl chloride (0.47 ml) in dichloromethane (5 ml). The reaction mixture is stirred for 1 hour and is then washed with water, dried over sodium sulfate and filtered through a silica-gel plug. The filtrate
- 10 is evaporated to afford the mesylate **37a** which is then dissolved in acetone (30 ml) containing sodium iodide (1.6 g). The reaction mixture is heated with stirring in an oil-bath (70° C) for 24 hours and then cooled. The insoluble salts are removed by filtration and the filtrate is evaporated under reduced pressure. The residual product is dissolved in
- 15 dichloromethane and washed with water, dried over sodium sulfate and filtered through a silica-gel plug. The filtrate is evaporated under reduced pressure to afford the title compound **38** as an oil (1.53 g), MS (FAB) m/e 280 (MH)<sup>+</sup>

### Step C

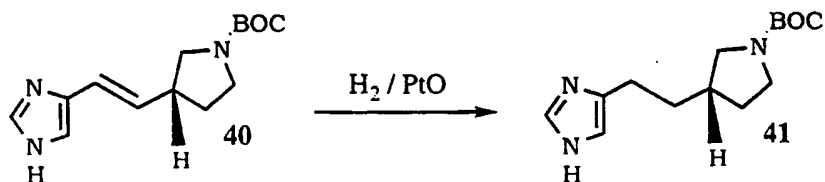


- 20 A solution of **38** (1.53 g) and triphenylphosphine (1.9 g) in dimethylformamide (10 ml) is heated in an oil-bath (90° C) for 24 hr. The reaction mixture is then evaporated under reduced pressure and the residual product is flash chromatographed on silica-gel (50 ml). Elution
- 25 with 10% methanol-dichloromethane afforded after evaporation under reduced pressure the title compound **39** as a white powder (1.56g), MS (FAB) m/e=446 (M)<sup>+</sup>.

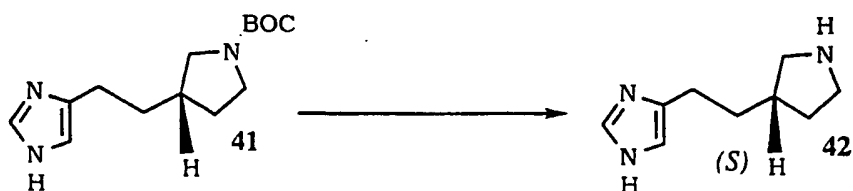
- 28 -

Step D

2.5 M butyllithium solution in hexanes (0.9 ml) is added to a solution of **39** (1.0 g) in tetrahydrofuran (10 ml) at  $-78^\circ$ . The solution is then stirred at room temperature for 30 minutes and the resulting solution is re-cooled to  $-78^\circ$  followed by the addition of a solution of the aldehyde (0.38 g) in tetrahydrofuran (5 ml). The reaction mixture is filtered and the filtrate is evaporated under reduced pressure. The resulting crude product is flash chromatographed on silica-gel (50 ml). Elution with 5% methanol-dichloromethane afforded after evaporation under reduced pressure the title compound **40** as a white powder (0.34 g), MS (FAB)  $m/e=264 \text{ (MH)}^+$

Step E

A solution of **40** (0.32 g) in ethanol (5 ml) containing PtO (0.085g) is hydrogenated at atmospheric pressure for 24 hours. The catalyst is then filtered and the filtrate is evaporated under reduced pressure. The resulting crude product is flash chromatographed on silica-gel (30 ml). Elution with 10% methanol-dichloromethane afforded after evaporation under reduced pressure the title compound **41** as a resinous gum (0.23 g), MS (FAB)  $m/e=266 \text{ (MH)}^+$ .

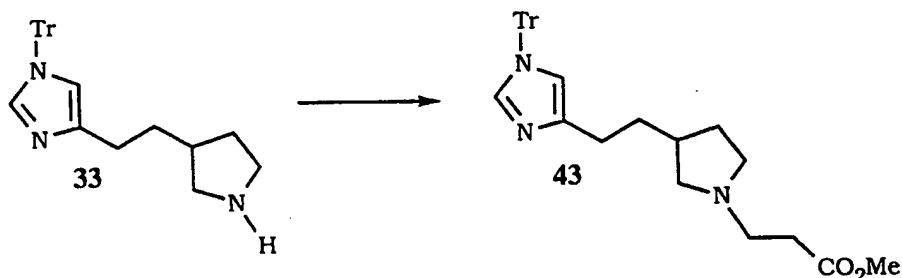
Step F

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Compound 41 (0.1 g) is stirred with 4M HCl in dioxane (2 ml) for 30 minutes and the reaction mixture is then evaporated under reduced pressure. The residual product is dissolved in methanol (2 ml) and the solution is stirred while adding Biorad AG 1-X8 (OH<sup>-</sup> form) ion-exchange resin until the pH of the solution is above 8. The resin is removed by filtration and the filtrate is then evaporated to afford the title compound 42 as a resinous gum (0.061 g), MS (Cl) m/e=165 (MH)<sup>+</sup>.

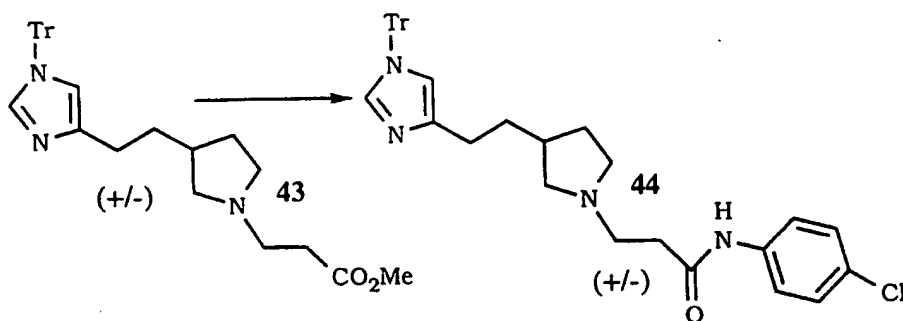
The R-enantiomer can be obtained in a similar manner.

10

EXAMPLE 2Step A

To a MeOH solution (15 ml) of 33 obtained in Step D of Example 1 (600 mg, 1.48 mmols) at r.t. was added methyl acrylate (0.300 ml, 3.33 mmols). The reaction mixture was stirred for 2h at r.t., then heated to 60°C overnight. The solvents were evaporated and the residue was chromatographed directly on silica gel (5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> → 10% MeOH) providing 574 mg (78%) of 43 as an off-white solid. LRMS (Cl, M+H) = 494.

20

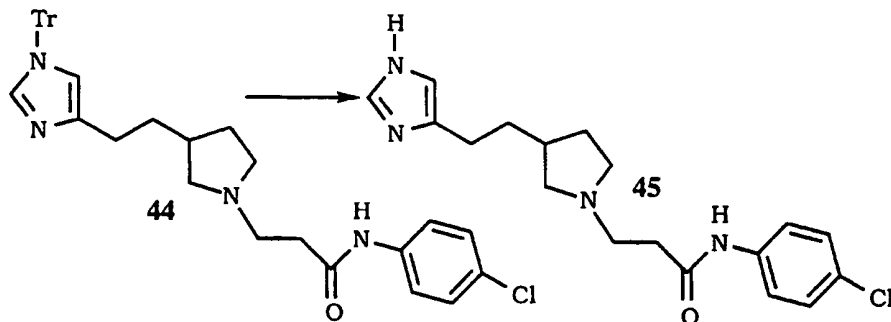
Step B



- 30 -

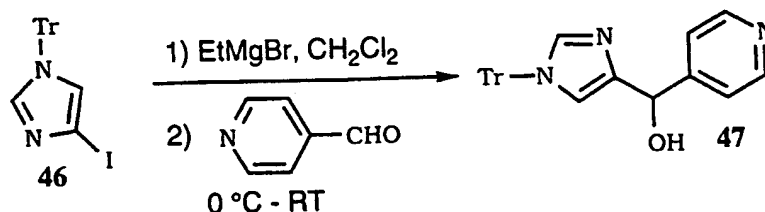
To a toluene (5 ml) solution of p-chloroaniline (0.160 g, 1.25 mmols) was added trimethylaluminum (0.700 ml, 2M in toluene) at 0°C. The mixture was stirred at 0°C for 15 min., and at r.t. for 40 min. Then a toluene-CH<sub>2</sub>Cl<sub>2</sub> solution of the compound **43** (10 ml, 1:1, v/v) was added at 0°C to the aniline complex. After 30 min., the mixture was heated to 80°C for 3h, and left at r.t. overnight. The reaction was quenched by the addition of solid Na<sub>2</sub>SO<sub>4</sub>·10 H<sub>2</sub>O, followed by the addition of MeOH. After stirring for 20 min., the mixture was filtered through celite, and concentrated under reduced pressure. Chromatography on silica gel (10% MeOH-EtOAc → 15% MeOH with 1% NH<sub>4</sub>OH) gives 624 mg (97%) of **44** as a white foam. *l*rms (Cl, M+H) = 589.

#### Step C

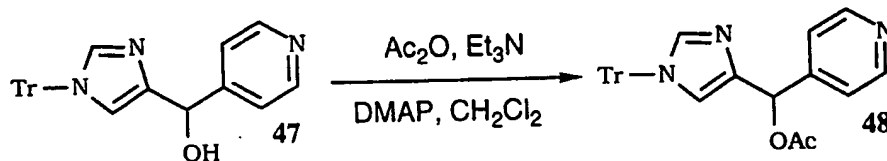


To a dioxane solution (10 ml) of the compound **44** from the previous step was added a solution of 4M HCl-dioxane (2 x 2 ml) and the mixture was heated to 80°C for 6h. The mixture was cooled to r.t., and evaporated under reduced pressure affording a gummy foam. The residue was rinsed with Et<sub>2</sub>O (3 x 10 ml) and the supernatant was decanted. The product was stored under high vacuum affording **45** as a tan solid (400 mg of dihydrochloride salt). MS(Cl) 347 (M+1).

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EXAMPLE 3Step A

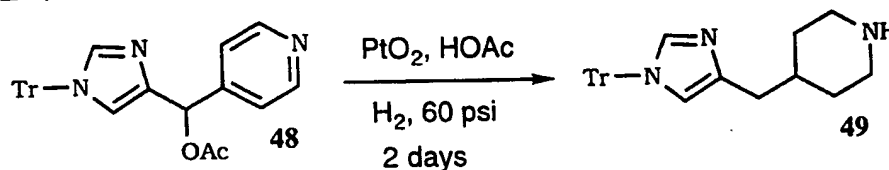
5 Ethylmagnesium bromide (23 mL, 69.1 mmol, 3M in ether) was dropwise added to a 0°C solution of 4-iodo-triphenylmethylimidazole (25.1 g, 57.6 mmol) in methylene chloride (280 mL). The mixture was stirred at 0°C for 30 min., the cooling bath was removed and the resulting yellow solution was stirred at room temperature for 60 min. 4-pyridine-  
 10 carboxaldehyde (6.1 ml, 63.4 mmol) was added dropwise. The reaction becomes very thick. A small aliquot of the reaction mixture is partitioned between ethyl acetate and saturated ammonium chloride. TLC (5% methanol/methylene chloride) indicated consumption of starting material. The reaction was quenched with saturated ammonium chloride. The resulting mixture was dissolved in methylene chloride (required ~1.5 L),  
 15 transferred to a separatory funnel, and extracted with methylene chloride. The extracts were combined, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated onto enough silica gel such that a free flowing powder was obtained. The powder was loaded onto a chromatography column prepacked with 10% methanol/methylene  
 20 chloride. Elution with the same solvent provided 22.5 g (93%) of **47** as a white solid. NMR <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>): 8.56( 2H, d, J=6.0 Hz), 7.47(1H, d, J=1.4 Hz), 7.36(11H, m), 7.13(6H, s), 6.63(1H, s), 5.79(1H, s), 4.43(1H, s). MS (CI): 418 (M+1, 26), 243(100), 167(45).

Step B

25 Acetic anhydride (9.7 mL, 51.4 mmol) was added to a room temperature suspension of **47** (21.4 g, 51.1 mmol), triethylamine (35.6 mL, 255.7 mmol) and dimethylaminopyridine (0.13 g, 1.0 mmol) in

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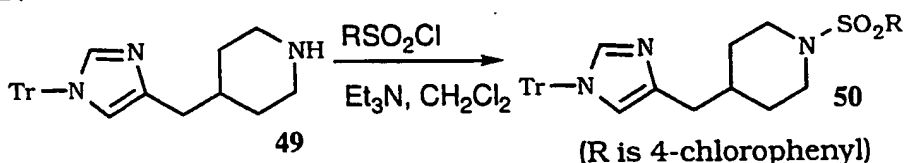
methylene chloride (800 mL). The suspension was allowed to stir overnight. All of the solid eventually dissolves. TLC (10% methanol/methylene chloride) indicated consumption of starting material. The mixture was transferred to a separatory funnel, diluted with methylene chloride, washed with saturated ammonium chloride and brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and the resulting residue was azeotroped (3X) with toluene (to remove residual acetic acid and acetic anhydride) to give 22.8 g (97%) of **48** as a white solid. NMR  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ): 8.61(2H, d,  $J=6.1$  Hz), 7.46(1H, d,  $J=1.4$  Hz), 7.38(11H, m), 7.15(6H, s), 6.83(1H, s), 6.80(1H, s), 2.20(3H, s).

Step C

**48** was dissolved in acetic acid (100 mL) with warming, transferred to a Parr hydrogenation flask and purged with nitrogen. Platinum oxide (1.13 g, 4.96 mmol) was added. The resulting mixture was hydrogenated on a Parr apparatus at 60 psi overnight. A small aliquot was quenched into 1 N NaOH and ethyl acetate. TLC (10% MeOH/methylene chloride) indicated consumption of starting material and the formation of lower  $R_f$  products. The mixture was resubmitted to hydrogenation for an additional day. TLC indicated consumption of starting material. The mixture was filtered through celite and concentrated. The residue was partitioned between 1N sodium hydroxide and methylene chloride. Solid sodium chloride was added to increase separation and the mixture was extracted with methylene chloride. The extracts were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated onto enough silica gel such that a free flowing powder results. This powder was loaded onto a chromatography column prepacked with silica and 10% methanol/methylene chloride. Elution with 5%  $\text{NH}_4\text{OH}$  (conc.)/10% methanol/85% dichloromethane to give 15.9 g (79%) of **49** as a white glass. NMR  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ): 7.33(10H, m), 7.14(6H, m), 6.51(1H, s),

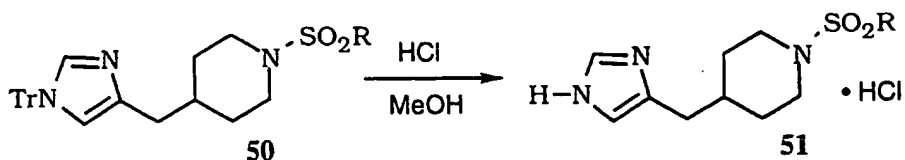
3.04(2H, m), 2.57(2H, dd, J=2.4, 12.1 Hz), 2.44(2H, d, J=7.0 Hz), 1.76(1H, m), 1.66(2H, d, J =12.5 Hz), 1.10(2H, dd, J=3.7, 12.4 Hz). MS (LC/MS): 408 (M<sup>+</sup>)

### Step D



5 4-<sup>4</sup>Chlorobenzenesulfonyl chloride (0.12 g, 0.56 mmol) was added to a room temperature solution of **49** (0.21 g, 0.51 mmol) and triethylamine (0.11 ml, 0.76 mmol) in methylene chloride (3 ml). The resulting mixture was stirred overnight. TLC (10 % methanol/methylene chloride) indicated consumption of starting material. The solution was transferred to a separatory funnel, diluted with methylene chloride, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated onto enough silica gel such that a free flowing powder was obtained. The resulting powder was loaded onto a chromatography column prepacked with silica and methylene chloride. Elution with methylene chloride followed by 10% methanol/methylene chloride gave 0.26 g of **50** as a white solid. NMR <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>): 7.68(2H, d, J=8.6 Hz), 7.49(2H, d, J=8.5 Hz), 7.32(10H, m), 7.12(6H, m), 6.49(1H, s), 3.74(2H, d, J=11.5 Hz), 2.41(2H, d, J=7.0 Hz), 2.24(2H, dd, J=2.36, 11.8 Hz), 1.69(2H, d, J=13.0 Hz), 1.61 (1H, m), 1.28(2H, dd, J=4.2, 12.8 Hz). MS (LC/MS): 582 (M+).

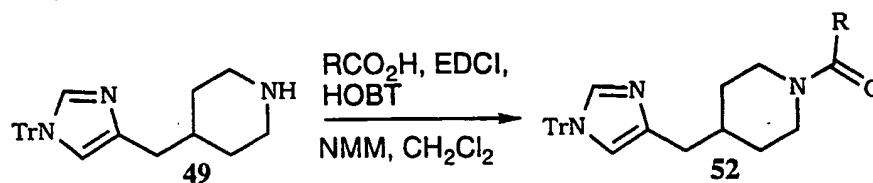
### Step E



25 A mixture of **50** (0.299 g, 0.56 mmol) in methanol (6 ml) and 1N HCl (3 ml) was warmed to 80°C. After 3h a small aliquot was quenched into 1N sodium hydroxide and ethyl acetate. TLC (10% methanol/methylene chloride) indicated consumption of starting material. The mixture was cooled to room temperature and concentrated. The residue was dissolved in water and ether and transferred to a separatory funnel. The water layer

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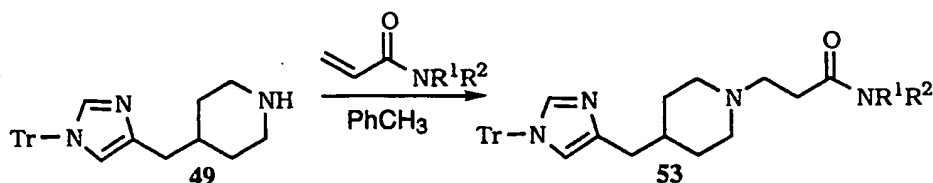
was washed with ether. The aqueous layer was concentrated to give 0.154 g (75%) of **51** as a glass. NMR  $^1\text{H}$  (400  $\text{CD}_3\text{OD}$ ): 8.80(1H, d,  $J=1.4$  Hz), 7.75(2H, d,  $J=8.8$  Hz), 7.62(2H, d,  $J=8.8$  Hz), 7.32(1H, s), 3.77( d,  $J=11.8$  Hz), 2.66(2H, d,  $J=7.2$  Hz), 2.29(2H, DT,  $J=2.5, 12.1$  Hz), 1.73(2H, d,  $J=11.7$  Hz), 1.60(1H, m), 1.32(2H, m). MS (CI): 340 (M+1)

**EXAMPLE 4****Step A**

**R** is 4-chlorophenyl. 1-3-(Dimethylaminopropyl)-3-ethylcarbo-diimide hydrochloride (0.20 g, 0.68 mmol) was added to a room temperature solution of **49** (0.21 g, 0.52 mmol), 4-chlorobenzoic acid (0.07 g, 0.57 mmol), N-methylmorpholine (0.17 ml, 1.56 mmol) and hydroxybenzotriazole (0.08 g, 0.62 mmol) in dimethylformamide (2 ml) and methylene chloride (2 ml). The resulting mixture was stirred overnight. TLC (10% methanol/methylene chloride) indicated consumption of starting material. The mixture transferred to a separatory funnel, diluted with methylene chloride, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated onto enough silica gel such that a free flowing powder was obtained. The resulting powder was loaded onto a chromatography column prepacked with silica and 10% methanol/methylene chloride. Elution with the same solvent gave 0.26 g of a clear oil. NMR shows the product was contaminated with dimethylformamide. The product was dissolved in ethyl acetate, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated to give 0.237 g (83%) of **52**. NMR  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ): 7.34(14H, m), 7.13(6H), 6.52(1H, s), 4.65(1H, m), 3.68(1H, m), 2.98(1H, m), 2.74(1H, m), 2.47(2H, d,  $J=7$  Hz), 1.96 (1H, m), 1.70(2H, m), 1.16(2H, m). MS (LC/MS): 546 (M+).

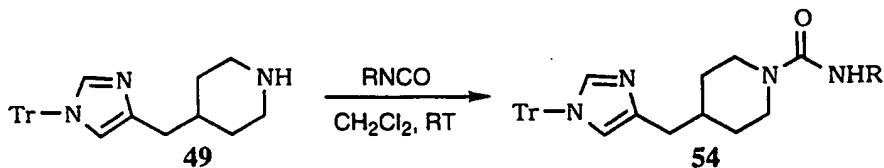
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EXAMPLE 5Step A

R<sup>1</sup> is H and R<sup>2</sup> is 4-chlorophenyl. A mixture of **49** (2.0 g, 4.9 mmol)  
 5 and N-(4-chlorophenyl)acrylamide (0.98 g, 5.4 mmol) in toluene (50 ml)  
 was heated to reflux overnight. TLC (10% methanol/methylene chloride)  
 indicated consumption of starting material. The mixture was cooled to  
 room temperature and concentrated onto enough silica gel such that a  
 free flowing powder was obtained. The resulting powder was loaded onto  
 10 a chromatography column prepacked with silica and 10%  
 methanol/methylene chloride. Elution with 10% methanol/methylene  
 chloride followed by 5% ammonia (conc)/10% methanol/85% methylene  
 chloride gave 1.17 g of the title compound with a trace of impurity and 1.50  
 g of pure **53** as oils. Combined yield 2.67 g (92%). NMR <sup>1</sup>H (400 MHz,  
 15 CDCl<sub>3</sub>): 7.46(2H, d, J=11.8 Hz), 7.34(1H, s), 7.32(10H, m), 7.23(2H, d,  
 J=11.8 Hz), 7.14(6H, m), 6.55(1H, s) 3.04(2H, d, J=15.3) 2.68(2H, m),  
 2.51(4H, d, J=8.3 Hz), 2.07(2H, t, J=14.7 Hz), 1.80(3H, m), 1.28 (2H, m).  
 MS (LC/MS): 589 (M<sup>+</sup>).

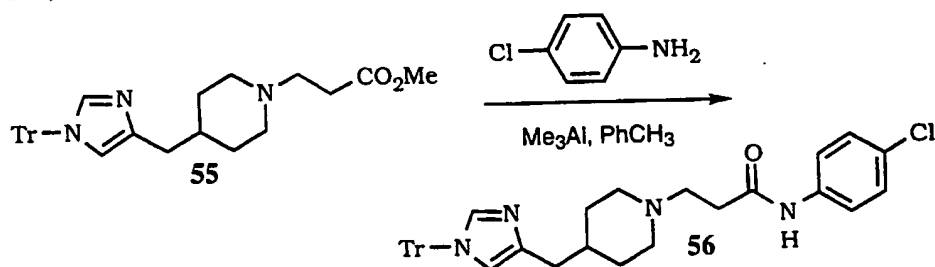
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EXAMPLE 6

R is 3,5-dichlorophenyl. 3,5-dichlorophenylisocyanate (0.21 g, 1.1  
 mmol) was added to a room temperature solution of **49** (0.3 g, 0.74 mmol)  
 in methylene chloride (5 ml). The resulting mixture was stirred overnight.  
 25 TLC (5% ammonia (conc)/10% methanol/85% methylene chloride)  
 indicated consumption of starting material. The mixture was concentrated  
 onto enough silica gel such that a free flowing powder was obtained. The  
 resulting powder was loaded onto a chromatography column prepacked

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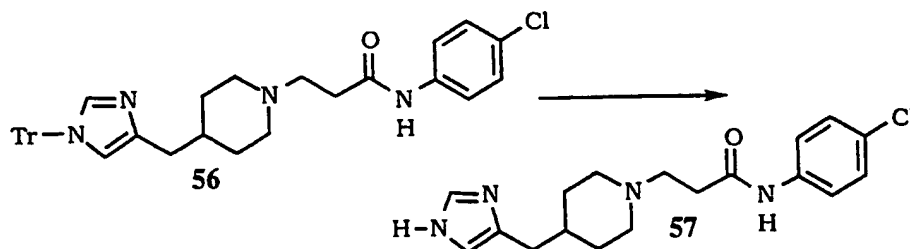
with silica and 20% acetone/methylene chloride. Elution with 20% acetone/methylene chloride followed by 5% methanol/methylene chloride gave 0.37 g (83%) of **54** as a white solid. NMR  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ): 7.53(1H, m), 7.36(10H, m), 7.12(6H, m), 6.97(1H, m), 6.71(1H, m), 6.56(1H, s), 4.04(2H, d,  $J=17.3$  Hz), 2.86(2H, m), 2.52(2H, d,  $J=9.1$  Hz), 1.95(1H, m), 1.72(2H, d,  $J=17.1$  Hz), 1.16(2H, m). MS (LC/MS): 596 (M+).

EXAMPLE 7Step A

Trimethylaluminum (1.2 ml, 2.4 mmol, 2M in toluene) was added to a 0°C solution of 3-chloroaniline (0.10g, 0.8 mmol) in toluene (7.5 ml). After 5 minutes the cooling bath was removed and the mixture was stirred at room temperature for 30 minutes. **55** (0.48 g, 0.1 mmol) in toluene (10 ml) was added via cannula. The mixture was refluxed overnight. TLC (10% methanol/85% methylene chloride) indicated consumption of starting material. The mixture was cooled to room temperature, diluted with ethyl acetate and quenched with a saturated solution of sodium sulfate. The resulting mixture was stirred overnight. The mixture was made basic with 1N NaOH (3 ml). The resulting mixture was transferred to a separatory funnel and extracted with ethyl acetate. The extracts were combined, washed with water and brine, dried over anhydrous sodium sulfate and concentrated onto enough silica gel such that a free flowing powder was obtained. The resulting powder was loaded onto a chromatography column prepacked with silica and 3% methanol/methylene chloride. Elution with 3-10% methanol/methylene chloride gave 0.31 g (66%) of **56** as a white Foam. NMR  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ): 7.71(1H, m) 7.29(12H, m), 7.14(6H, m), 7.05(2H, m), 6.55(1H, s),

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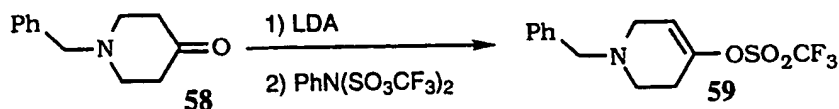
3.04(2H, m), 2.68(2H, m), 2.51(3H, m), 2.09(2H, m), 1.81(2H, m), 1.58(2H, m), 1.3(2H, m). MS (LC/MS): 589 (M+).

Step B

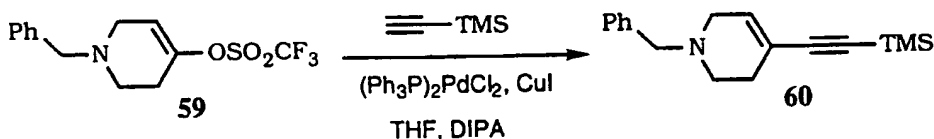
- 5           Compound 56 (0.6 g, 1.0 mmol) in methanol (18 ml) and 1N HCl (6 ml) was warmed to 60°C. Progress of the reaction was monitored by quenching a small aliquot of the reaction with 1N sodium hydroxide and ethyl acetate. TLC (5% ammonia(conc)/10% methanol/85% methylene chloride) indicated consumption of starting material. The mixture was
- 10 cooled to room temperature and concentrated. The residue was not totally soluble in ether/water. The residue was made basic with 1N NaOH, diluted with methylene chloride, transferred to a separatory funnel and extracted with methylene chloride. The extracts were combined, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated
- 15 onto enough silica gel such that a free flowing powder was obtained. The powder was loaded onto a chromatography column prepacked with silica and 10% methanol/methylene chloride. Elution with 10% methanol/methylene chloride followed by 5% ammonia(concentrated)/10% methanol/ chloride) gave the title compound
- 20 as a clear oil. The oil was redissolved in methylene chloride and treated with an excess of HCl (4M in dioxane) and concentrated in vacuum to give 0.205 g (44%) of 57 as a clear glass. NMR <sup>1</sup>H (400 CD<sub>3</sub>OD): 8.85(1H, s), 7.50(2H, d, J=11.4 Hz), 7.40(1H, s), 7.05(2H, d, J=11.4 Hz), 4.251(2H, s), 4.15(2H, t, J=7.5 Hz), 3.46(2H, d, J=16.2 Hz), 3.35(3H, m), 3.02(2H, t, J=16.2 Hz), 2.95(6H, s), 2.74(2H, d, J=9.0 Hz), 2.25(2H, m), 1.93(2H, d, J=16.2 Hz), 1.60(2H, m). MS (FAB): 357 (M+1).
- 25



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EXAMPLE 8Step A

- 5 n-butyl lithium (30.4 ml, 48.6 mmol, 1.6 M in hexane) was added to a -78°C solution of diisopropyl amine (6.63 ml, 50.6 mmol) in tetrahydrofuran (75 ml). After 30 minutes **58** (7.5 ml, 40.5 mmol) in tetrahydrofuran (30 ml) was added slowly via cannula. The reaction was stirred at -78°C for 1.5 hours, then N- phenyltrifluoromethanesulfonamide (15.3 g, 44.5 mmol) in tetrahydrofuran (50 ml) was added via cannula.
- 10 The mixture was allowed to warm to room temperature overnight. TLC (20% ethyl acetate/hexanes) indicated consumption of starting material. Triethylamine (added to prevent acid hydrolysis of the triflate on silica gel) was added and the resulting mixture was concentrated onto enough silica gel such that a free flowing powder was obtained. The powder was
- 15 loaded onto a chromatography column prepacked with silica and 20% ethyl acetate/hexanes. Elution with the same solvent provided 10.8 g (83%) of **59** as a yellow oil. NMR <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>): 7.30(5H, m), 5.73(1H, m), 3.63(2H, s), 3.13(2H, dd, J=3.0, 6.4 Hz), 2.72(2H, t, J =5.7 Hz), 2.45(2H, m).

20 Step B

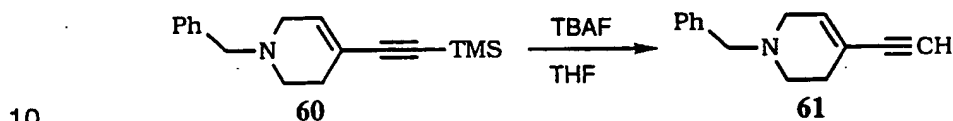
- Trimehtylsilylacetylene (5.9 ml, 42.1 mmol) was added to a room temperature solution of **59** (10.8 g, 33.7 mmol) in a 3:1 mixture of
- 25 tetrahydrofuran and diisopropylamine (50 ml). Dichlorobis(triphenylphosphine)palladium (II) (1.42 g, 2.0 mmol) and copper (I) iodide (1.1 g, 5.7 mmol) were added. The color of the reaction progressed from red to brown to black. After 1 hour, TLC (5% ethyl acetate/hexanes) indicated consumption of starting material. The reaction was diluted with ethyl
- 30 ether, transferred to a separatory funnel, washed with water, 3/1 saturated

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ammonium chloride/ammonia (conc) and brine, dried over anhydrous sodium sulfate, filtered and concentrated onto enough silica gel such that a free flowing powder was obtained. The powder was loaded onto a chromatography column prepacked with silica and 10% ethyl

5 acetate/hexanes. Elution with the same solvent provided 6.1 g (67%) of **60** as a yellow solid. NMR  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ): 7.35(5H, m), 6.14(1H, m), 3.63(2H, s), 3.08(2H, m), 2.63(2H, t,  $J = 5.7$  Hz), 2.33(2H, m), 0.23(9H, s).

### Step C

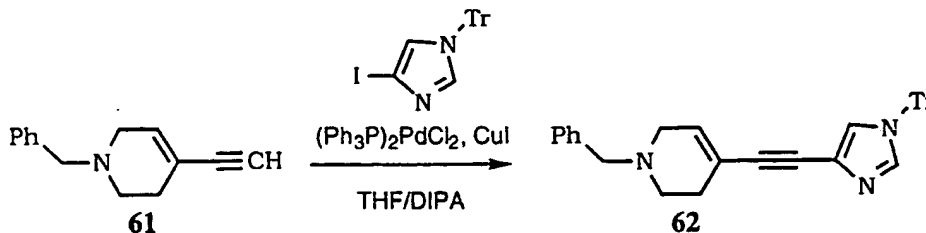


Tetrabutylammonium fluoride (27 ml, 27.0 mmol, 1M in tetrahydrofuran) was added to a room temperature solution of **60** (6.1 g, 22.5 mmol) in tetrahydrofuran (100 ml). After ~2 hours, TLC (20% ethyl acetate/hexanes) indicated consumption of starting material. The reaction

15 mixture was diluted with ethyl acetate, transferred to a separatory funnel, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated onto enough silica gel such that a free flowing powder was obtained. The powder was loaded onto a chromatography column prepacked with silica and 10% ethyl acetate/hexanes. Elution

20 with the same solvent provided 3.4 g (76%) of **61** as a yellow solid. NMR  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ): 7.36(5H, m), 6.17(1H, m), 3.65(2H, s), 3.11(2H, m), 2.91(1H, s), 2.64(2H, t,  $J = 5.6$  Hz), 2.35(2H, m).

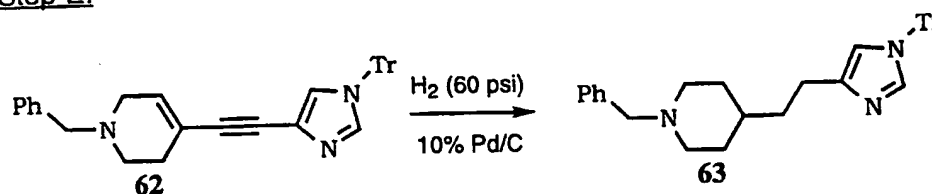
### Step D



**61** (3.42 g, 17.3 mmol) and 1-triphenylmethyl-4-iodoimidazole (6.3 g, 14.4 mmol) were dissolved in tetrahydrofuran (100 ml) and diisopropylamine (40 ml). Dichlorobis(triphenylphosphine)palladium (II) (1.22 g, 1.7 mmol) and copper (I) iodide (0.4 g, 1.7 mmol) were added. The reaction

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mixture was allowed to stir at room temperature overnight. TLC (5% methanol/methylene chloride) indicated consumption of starting material. The reaction was diluted with methylene chloride, transferred to a separatory funnel, washed with water, 3/1 saturated ammonium chloride/ammonia (conc) and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was recrystallized from ethyl acetate to give 7.02 g (98%) of **62** as a slightly yellow solid. NMR <sup>1</sup>H (400 MHz, CDCl<sub>3</sub>): 7.44(1H, d, J=1.1 Hz), 7.40(14H, m), 7.18(6H, m), 7.06(1H, d, J=1.5 Hz), 6.12(1H, m), 3.64(2H, s), 3.12(2H, m), 2.64(2H, t, J=5.7 Hz), 2.39(2H, m). MS(FAB): 505 (M+).

Step E.

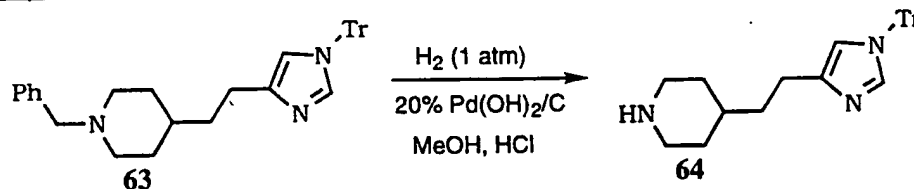
**62** (7.0 g, 14.1 mmol) was dissolved in a mixture of tetrahydrofuran (250 ml), methanol (200 ml) and methylene chloride (100 ml) and purged with nitrogen. 10% palladium on carbon (1.0 g) was added and the resulting suspension was hydrogenated on a Parr apparatus overnight at 60 psi. TLC (5% methanol/methylene chloride) indicated a considerable amount of remaining starting material. The mixture was filtered through celite, fresh 10% palladium on carbon was added and the mixture was again hydrogenated on a Parr apparatus at 60 psi for two days. TLC (5% methanol/methylene chloride) indicated a considerable amount of remaining starting material. 20% palladium hydroxide on carbon (1.0 g) and acetic acid (60 ml) were added and the mixture was again hydrogenated on a Parr apparatus at 60 psi overnight. The mixture was filtered and concentrated. TLC (5% ammonia (conc)/10% methanol/methylene chloride) indicated a number of new spots. The residue was redissolved in acetic acid (75 ml) and 20% palladium hydroxide on carbon (1.0 g) was added and the mixture was hydrogenated at 50 psi for two days. The reaction was filtered through celite, the filter cake was well washed with methanol. The filtrate was concentrated and the residue was azeotroped with toluene (3X) to remove

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residual acetic acid. The residue was dissolved with 1N NaOH and methylene chloride, transferred to a separatory funnel and extracted with methylene chloride. The extracts were combined, washed with water and brine, dried over anhydrous sodium sulfate and concentrated to provide

- 5 6.8 g of an amber oil. Chromatography on silica eluting with 4% ammonia(conc)/10% methanol/86% methylene chloride provided 0.7 g (10%) of **63**. NMR  $^1\text{H}$  (400 MHz,  $\text{CD}_3\text{Cl}_3$ ): 7.29(15H, m), 7.13(6H, m), 6.49(1H, s), 3.58(2H, m), 2.94(2H, m), 2.54(2H, t,  $J = 8.0$  Hz), 1.98(2H), 1.66(2H, m), 1.54(3H, m), 1.29(2H).

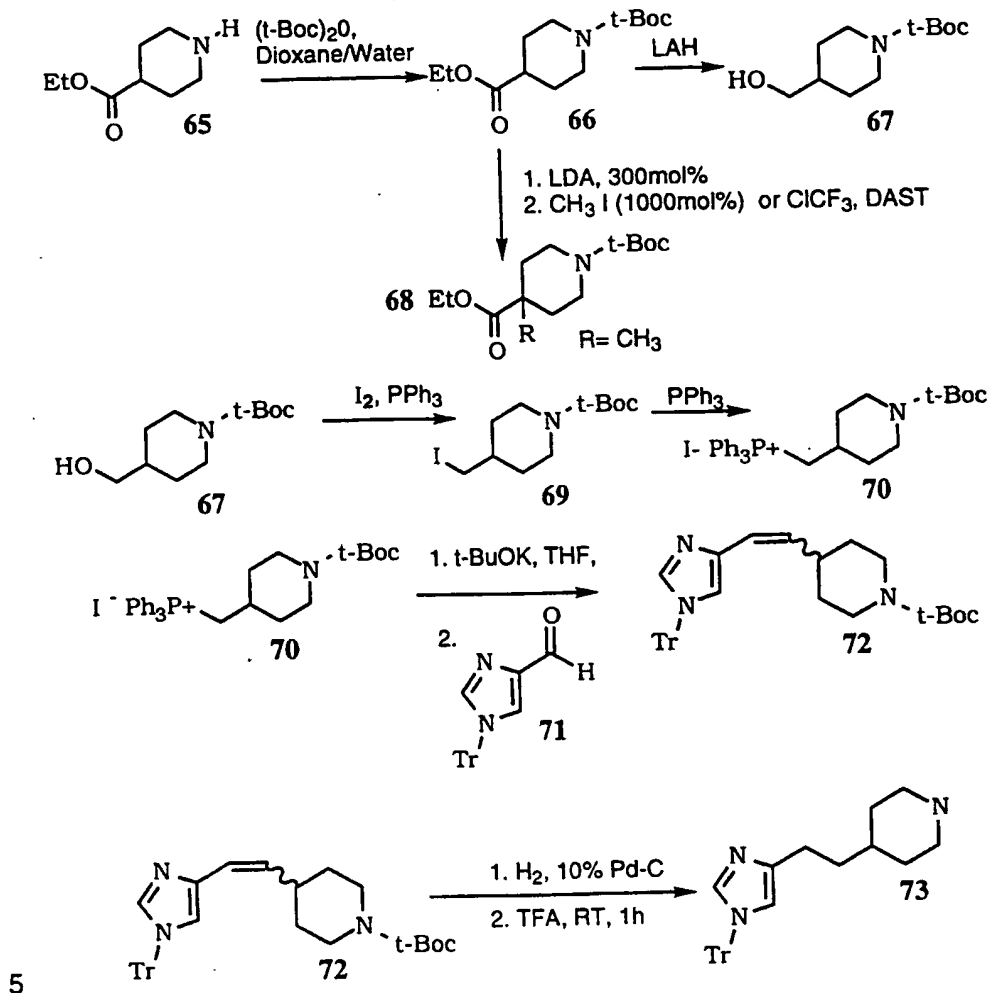
10 Step F



- 63** (0.019 g, 0.054 mmol) was dissolved in methanol (1 ml), 1M HCl (2 drops) was added. The resulting solution was purged with nitrogen. 10% palladium on carbon (0.005 g) was added and the mixture was
- 15 stirred under a balloon of hydrogen gas overnight. The mixture was filtered through celite, the filter cake was well washed with methanol and concentrated to give 0.0128 g of a clear oil.  $^1\text{H}$  NMR analysis indicated no reaction had occurred. The oil was redissolved in methanol (1 ml), HCl (1 drop) was added. The resulting solution was purged with nitrogen. 20%
- 20 palladium hydroxide on carbon (0.01 g) was added and the mixture was stirred under a balloon of hydrogen gas overnight. The mixture was filtered through celite, the filter cake was well washed with methanol and concentrated to give 0.0085 g of **64** as a clear oil. NMR  $^1\text{H}$  (400 MHz,  $\text{CD}_3\text{OD}$ ): 8.87(1H, s), 7.41(1H, s), 3.45(2H, m), 3.04(2H, m), 2.85(2H, m),
- 25 2.05(2H, m), 1.75(3H, m), 1.53(3H, m).

Compound (**64**) was then used to produce compounds of formula I, e.g. by following the procedures of the examples above.

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**EXAMPLE 9**

5

Commercially available ethyl isonipecotatate was protected with di-tert-butyl dicarbonate, the ethyl ester reduced with lithium aluminum hydride and the intermediate alcohol was transformed into the desired iodide **69** with iodine according to the procedure described by A.

10 Villalobos in the Journal of Medicinal Chemistry **1994**, 37, 2721-2734.

A 500 mL round bottomed flask was charged with iodide **69** (10.0g, 30.75 mmol), triphenylphosphine (16.9g, 64.6 mmol) and 150 mL acetonitrile.

The solution was heated at reflux for 16h, cooled to room temperature and then concentrated in vacuo to a yellow oil. The crude product was further purified by chromatography on silica using a gradient from 4:1 hexane: ethyl acetate to 100% ethyl acetate and final elution with

15

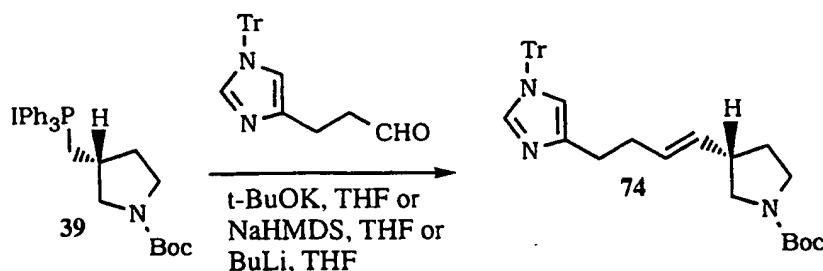
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95:5 methylene chloride: methanol to afford phosphonium salt **70** (7.13 g) in 40% yield.

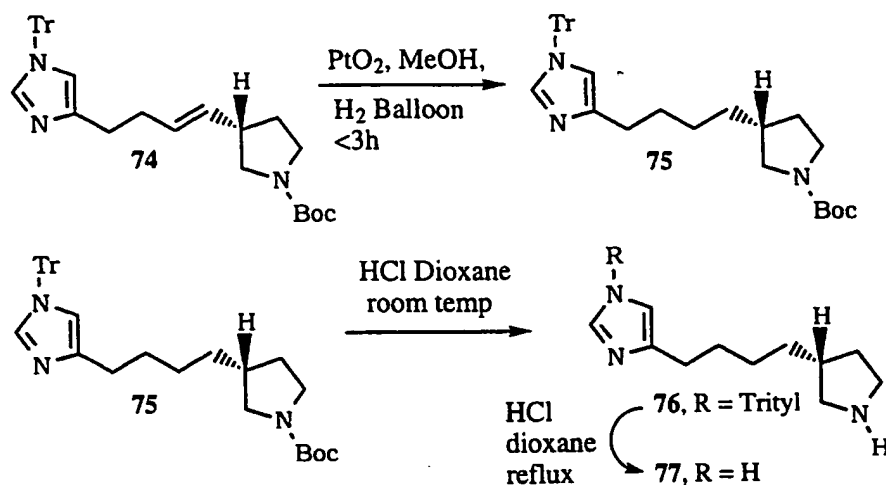
A 500 mL round bottomed flask was charged with phosphonium salt **70** (7.13g, 12.14 mmol), n-trityl imidazole-4-carboxaldehyde (4.5g, 13.14 mmol) and 250 mL dry tetrahydrofuran and the reaction mixture was cooled to 4°C. Potassium t-Butoxide (14 ml of a 1 M in Dioxane, 14 mmol) was added dropwise and the solution was allowed to warm slowly to room temperature and the disappearance of aldehyde was monitored by TLC. Additional potassium t-butoxide was added at 4 h (2.4 mL, 2.4 mmol) and the reaction was allowed to stir at room temperature. After a total of 16 h the reaction was filtered and the filtrate was concentrated to an oil. Elution on silica gel column with hexanes: ethyl acetate afforded pure alkene **72** (3.2g) in 51% yield as a mixture of E/Z isomers.

A 500 mL round bottomed flask was charged with alkene **72** (3.2 g), PtO<sub>2</sub> (0.75g), and 150 mL methanol and affixed with a three-way stopper with a hydrogen bladder. The heterogeneous reaction was stirred under hydrogen for 2 h. The catalyst was filtered and the filtrate was concentrated to an oil (3.2g). The crude intermediate was redissolved in 180 mL dioxane and treated at room temperature with 1 M TFA in dioxane (20 mL, 20 mmol) for 24 h. The pH of the reaction mixture was adjusted to greater than 8 with sodium hydroxide (1M), ethyl acetate was added and the layers were separated. The organic layer was washed with brine, dried over magnesium sulfate and concentrated to a semi-solid. The crude product was purified by chromatography (methylene chloride: methanol eluent) to afford pure **73** (1.8 g, 69% yield).

#### EXAMPLE 10



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To a flask containing the phosphonium salt **39** (3.5 g, 6.11 mmol) was added dry THF (30 mL) under a nitrogen atmosphere. The mixture was cooled to 0°C and t-BuOK was added (1.0 M solution, 8 g, 8 mmols) dropwise via syringe. The resulting yellow mixture was stirred for 20 min, then the 3-carbon aldehyde (2.4 g, 6.55 mmol) was added in 8 mL THF via syringe. The reaction mixture was stirred for 24 h at 25°C then quenched by the addition of  $\text{NH}_4\text{Cl}$  solution. The aqueous portion was extracted with EtOAc. The combined organics were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated. Chromatography on silica gel (40% EtOAc-hexane → 60% EtOAc) afforded **74** 2.6 g (71%) of material. MS (electrospray,  $\text{M}+\text{H}$ ) = 534.

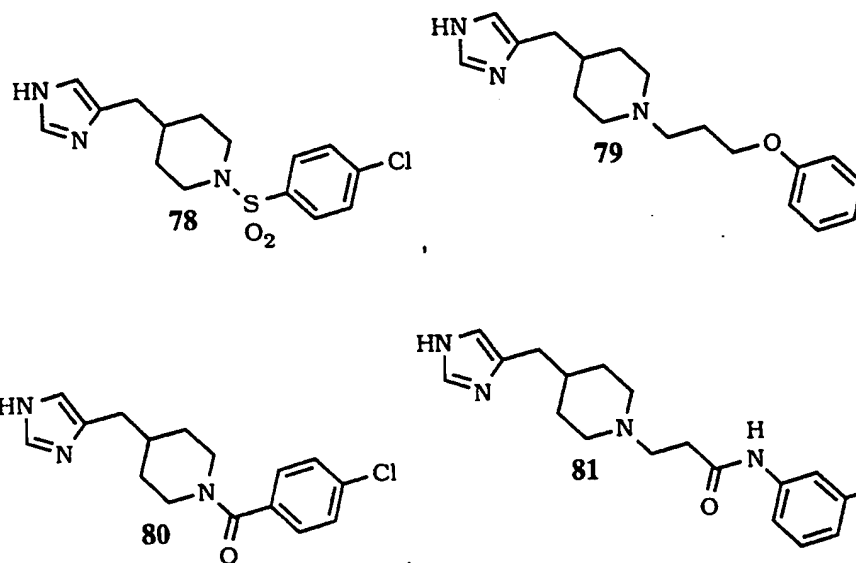
To Compound **74** (2.3g, 4.3 mmol) dissolved in MeOH was added  $\text{PtO}_2$  (0.4 g). A hydrogen balloon was placed over the reaction mixture, and stirring was continued for 2-3 h at 25°C. The reaction mixture was then chromatographed on  $\text{SiO}_2$  (100% hexane increasing to 75% EtOAc-hexane) to remove the catalyst and obtain the pure product **75**, 2.24 g (97%). MS (electrospray,  $\text{M}+\text{H}$ ) = 536.

To a dioxane solution of compound **75** (2.0 g, 3.7 mmol) was added a 4M HCl-dioxane solution (10 mL) at 25°C. The mixture was stirred for about 6 h, then cooled to 0°C, and 5% NaOH was added to bring the pH to 7. The mixture was extracted with EtOAc, and the combined organics were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated, to give 1.14 g (100%) of compound **76**. MS (electrospray,  $\text{M}+\text{H}$ ) = 436.

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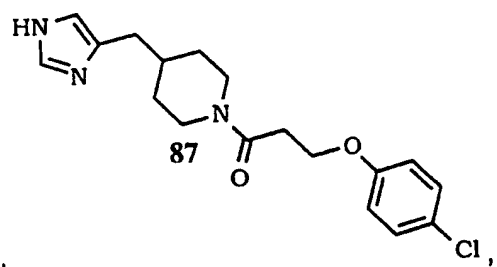
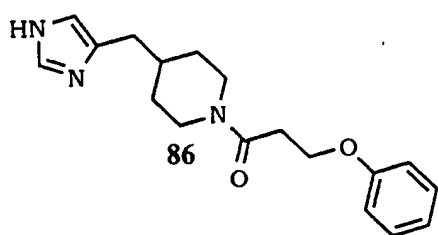
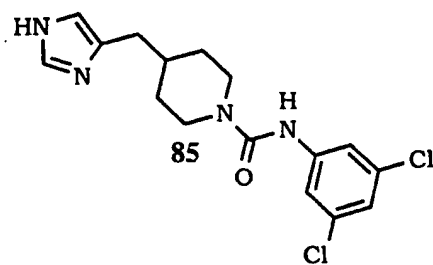
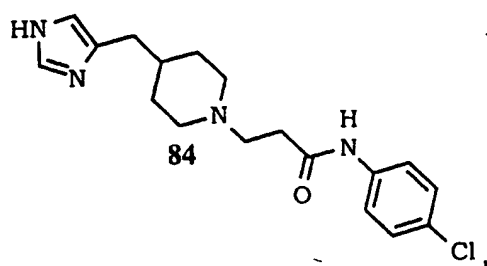
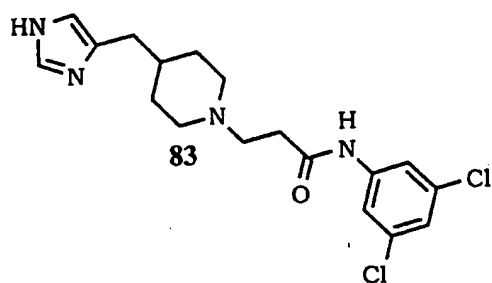
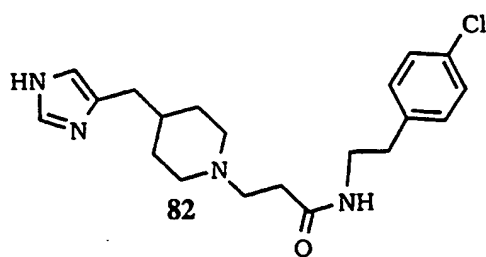
Treatment of **76** ( 200 mg, 0.46 mmol) again with 4M HCl-dioxane (5 mL) at 80°C for 4 h affords 140 mg of compound **77**. MS (CI, M+H) = 194.

- 5 The compounds below were prepared following procedures similar to those described above.

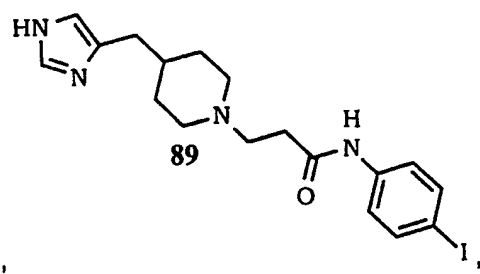
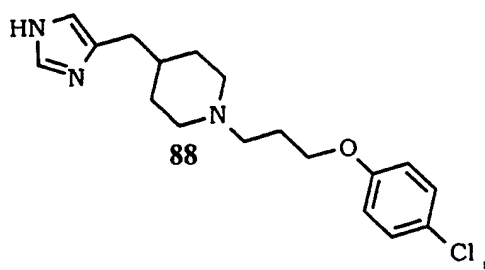




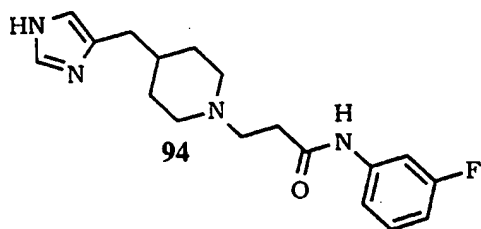
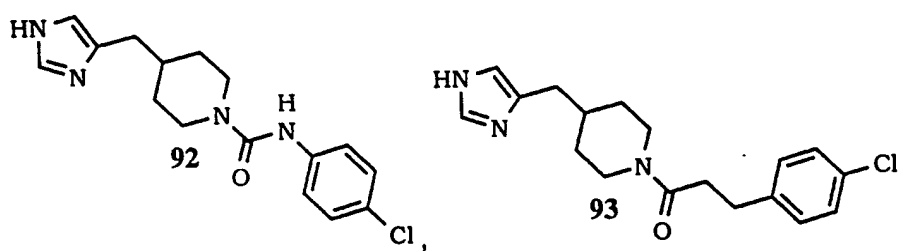
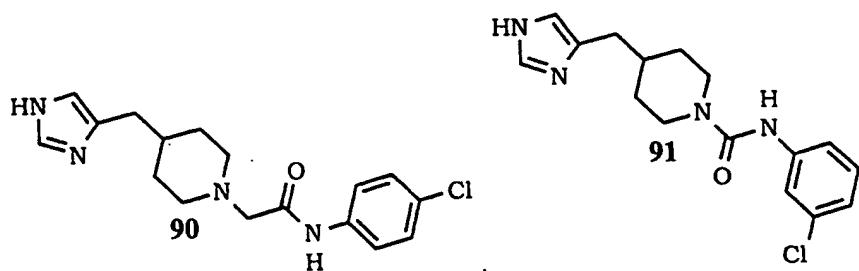
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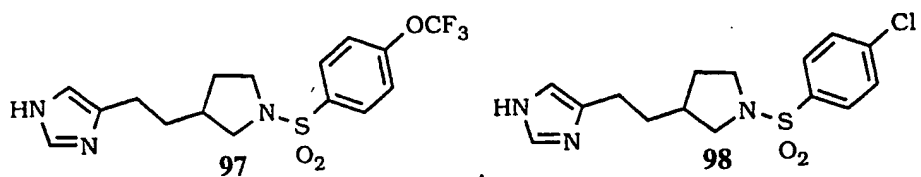
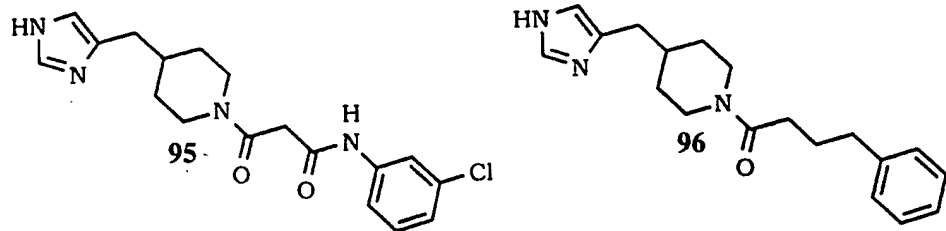
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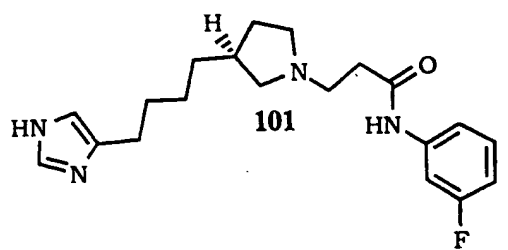
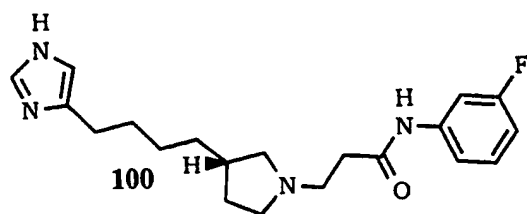
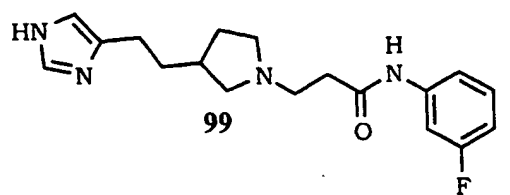
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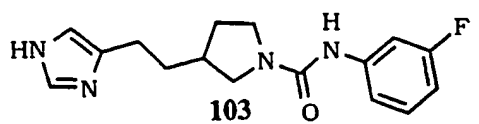
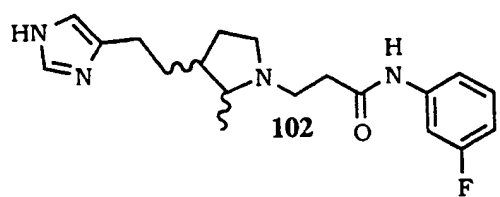
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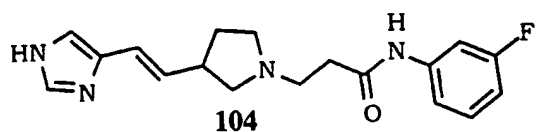
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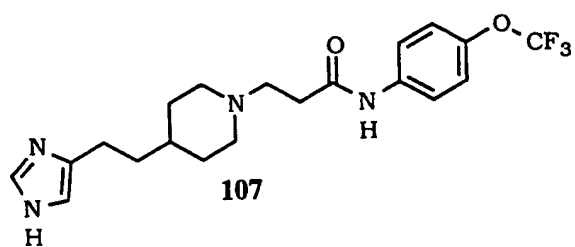
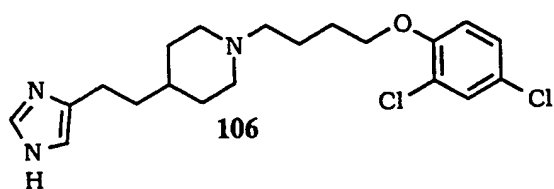
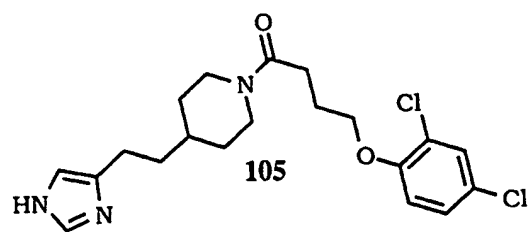
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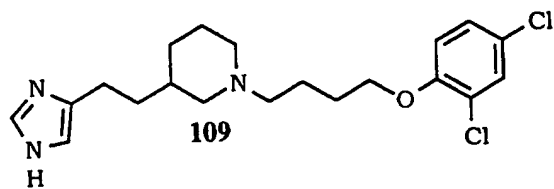
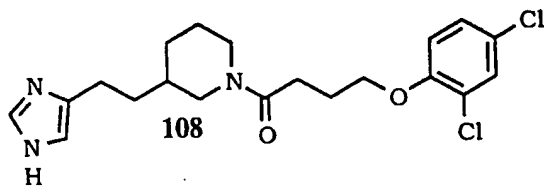
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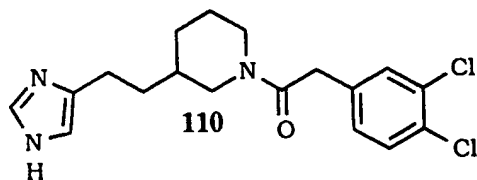
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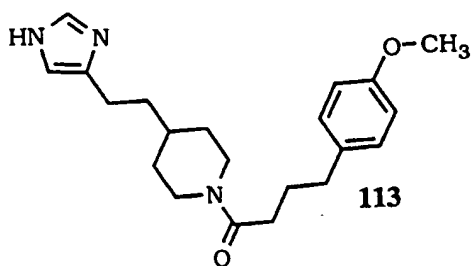
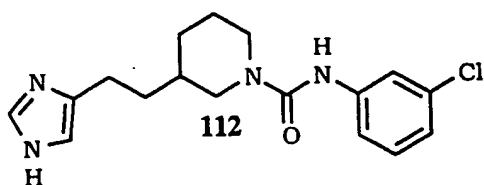
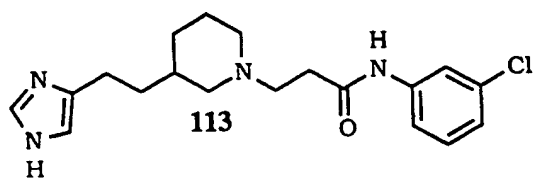
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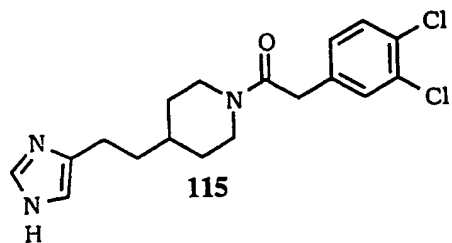
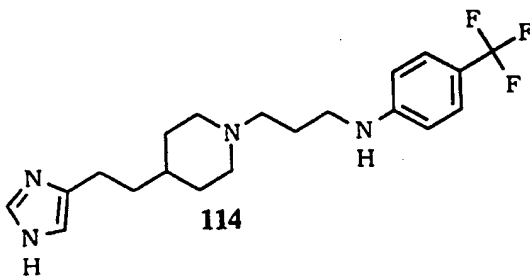
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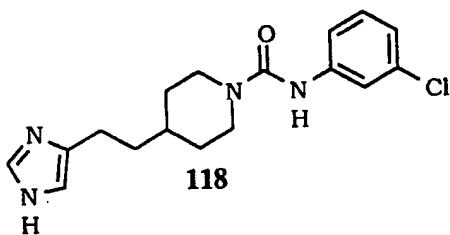
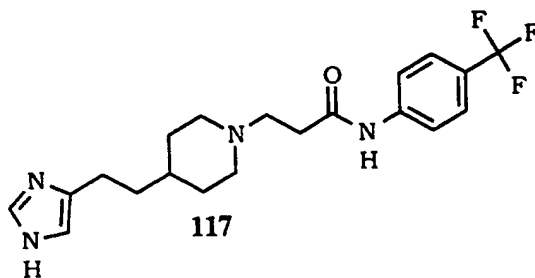
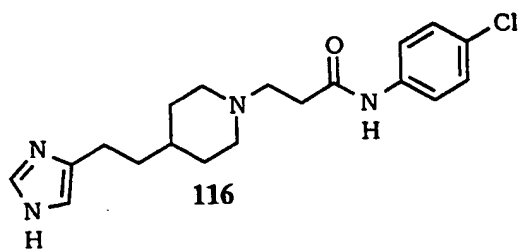


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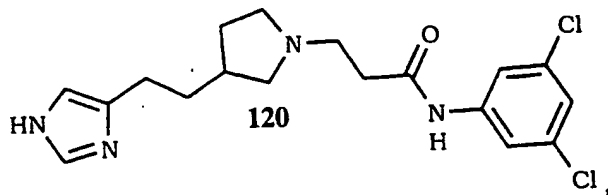
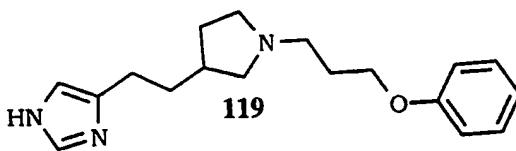


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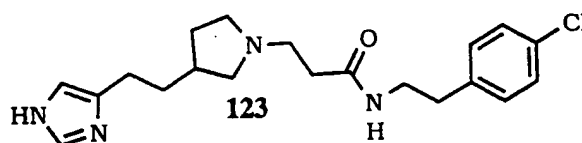
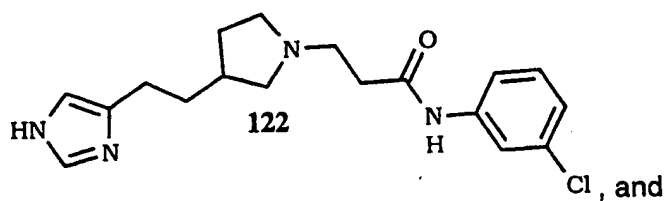
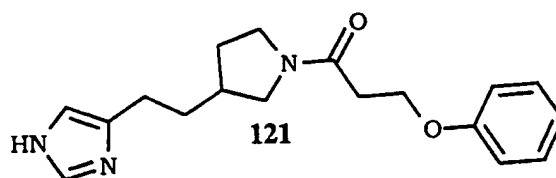


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MASS SPECTROMETRY DATA

| COMPOUND NO. | MASS SPEC       | COMPOUND NO. | MASS SPEC                 |
|--------------|-----------------|--------------|---------------------------|
| 78           | (CI) 340 (M+1)  | 79           | (FAB) 300 (M+1)           |
| 80           | (CI) 304 (M+1)  | 81           | (EI) 346 (M+)             |
| 82           | (EI) 374 (M+)   | 83           | (EI) 380 (M+)             |
| 84           | (CI) 347 (M+1)  | 85           | (CI) 353 (M+1)            |
| 86           | (EI) 313 (M+)   | 87           | (EI) 347 (M+)             |
| 88           | (EI) 333 (M+)   | 89           | (CI) 439 (M+1)            |
| 90           | (FAB) 333 (M+1) | 91           | (FAB) 319 (M+1)           |
| 92           | (FAB) 319 (M+1) | 93           | (FAB) 332 (M+1)           |
| 94           | (FAB) 331 (M+1) | 95           | (FAB) 361 (M+1)           |
| 96           | (FAB) 312 (M+1) | 97           | (CI) 390 (M+1)            |
| 98           | (CI) 340 (M+1)  | 99           | (CI) 331 (M+1)            |
| 100          | (CI) 359 (M+1)  | 101          | Electrospray<br>359 (M+1) |

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|     |   |       |   |
|-----|---|-------|---|
| 102 | Electrospray<br>345 (M+1)                           | 103   | FAB 303 (M+1)                                       |
| 104 | (Cl) 329 (M+1)                                      | 105   | High Resolution<br>Calc. 410.1402<br>Found 410.1410 |
| 106 | High Resolution<br>Calc. 396.1609<br>Found 396.1618 | ----- | -----   |

The compounds of this invention are either agonists or antagonists of the histamine H<sub>3</sub> receptor. The binding affinity of the compounds of the invention to the H<sub>3</sub> receptor may be demonstrated by the procedure

5 described below:

#### H<sub>3</sub> Receptor Binding Assay

The source of the H<sub>3</sub> receptors in this experiment was guinea pig brain. The animals used weighed 400-600 g. The tissue was homogenized using a Polytron in a solution of 50 mM Tris, pH 7.5. The  
10 final concentration of tissue in the homogenization buffer was 10% w/v. The homogenates were centrifuged at 1000 x g for 10 min. in order to remove clumps of tissue and debris. The resulting supernatants were then centrifuged at 50,000 x g for 20 min. in order to sediment the membranes, which were next washed 3 times in homogenization buffer  
15 (50,000 x g for 20 min. each). The membranes were frozen and stored at -70°C until needed.

All compounds to be tested were dissolved in DMSO and then diluted into the binding buffer (50 mM Tris, pH 7.5) such that the final concentration was 2 µg/ml with 0.1% DMSO. Membranes were then  
20 added (400 µg of protein) to the reaction tubes. The reaction was started by the addition of 3 nM [<sup>3</sup>H]R-α-methylhistamine (8.8 Ci/mmol) or [<sup>3</sup>H]-N-methylhistamine (80 Ci/mmol) and incubated at 30° for 30 min. Bound ligand was separated from unbound ligand by filtration, and the amount of radioactive ligand bound to the membranes was quantitated by liquid  
25 scintillation spectrometry. All incubations were performed in duplicate and



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the standard error was less than 10% in all instances. Compounds that inhibited greater than 70% of the specific binding of radioactive ligand to the receptor were serially diluted to determine a  $K_i$  (nM).

Compounds 45, 78, 79, 81-97, and 113-118 had a  $K_i$  in the range of 0.1 to 220 nM. Compounds 45, 79, 81, 82, 83, 84, 86, 87, 88, 89, 91, 94, 96, and 116 had a  $K_i$  in the range of 0.1 to 20 nM.

Compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal

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patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form.

- 5 In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from  
10 about 1 mg to 500 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which  
15 are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of  
20 the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 1 mg to 2000 mg/day preferably 10 to 1000  
25 mg/day, in one to four divided doses to achieve relief of the symptoms. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. As used therein, the term "active  
30 compound" is used to designate one of the compounds of the formula I or salt thereof. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

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Pharmaceutical Dosage Form ExamplesEXAMPLE ATablets

| <u>No.</u> | <u>Ingredients</u>  | <u>mg/tablet</u> | <u>mg/tablet</u> |
|------------|---|------------------|------------------|
| 1.         | Active compound   | 100              | 500              |
| 2.         | Lactose USP   | 122              | 113              |
| 3.         | Corn Starch, Food Grade,<br>as a 10% paste in<br>Purified Water | 30               | 40               |
| 4.         | Corn Starch, Food Grade   | 45               | 40               |
| 5.         | Magnesium Stearate  | <u>3</u>         | <u>7</u>         |
|            | Total   | 300              | 700              |

Method of Manufacture

- 5 Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

10

EXAMPLE BCapsules

| <u>No.</u> | <u>Ingredient</u>       | <u>mg/capsule</u> | <u>mg/capsule</u> |
|------------|-------------------------|-------------------|-------------------|
| 1.         | Active compound         | 100               | 500               |
| 2.         | Lactose USP             | 106               | 123               |
| 3.         | Corn Starch, Food Grade | 40                | 70                |
| 4.         | Magnesium Stearate NF   | <u>4</u>          | <u>7</u>          |
|            | Total                   | 250               | 700               |

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Method of Manufacture

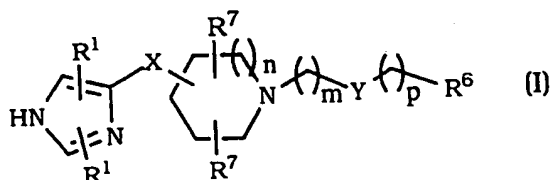
Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating  
5 machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those  
10 of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

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WHAT IS CLAIMED IS:

1. A compound of the formula:



5

or pharmaceutically acceptable salts or solvates thereof, wherein:

X is a straight chain alkyl group having 1 to 7 carbon atoms or an alkene or alkyne group with 2 to 4 carbon atoms; wherein said alkyl or alkene groups are optionally substituted with up to two R<sup>7</sup> groups;

10

n is 0, 1 or 2 ,

m is 0 to 4;

p is 0 to 4;

when m is 0 to 4, Y represents -SO<sub>2</sub>-; -CS-; -CO-; -CONR<sup>5</sup>-;

-CO(CH<sub>2</sub>)<sub>w</sub>O- (with w being 1 to 4); -COO-; -CON(OR<sup>5</sup>)-; -C(NR<sup>5</sup>)NR<sup>5</sup>-;

15

-SO<sub>2</sub>NR<sup>5</sup>- or -CSNR<sup>5</sup>-;

when m is 2 to 4, Y represents all the groups above when m is 0 to

4 and, in addition, Y represents -CHOR<sup>5</sup>-; -O-; -NR<sup>5</sup>CONR<sup>5</sup>-; -NR<sup>5</sup>CO-;

-NR<sup>5</sup>-; -OCONR<sup>5</sup>-; -NR<sup>5</sup>C(NR<sup>5</sup>)NR<sup>5</sup>-; -NR<sup>5</sup>CSNR<sup>5</sup>-; -NR<sup>5</sup>CS- or -NR<sup>5</sup>SO<sub>2</sub>-;

-NR<sup>5</sup>C(O)O-; or -CSNR<sup>2</sup>-;

20

each R<sup>5</sup> independently represents hydrogen, alkyl or benzyl;

R<sup>6</sup> is selected from:

(1) aryl,

(2) heteroaryl,

(3) a 3-7 membered heterocyclic group,

25

(4) substituted aryl having 1-3 substituents independently

selected from of alkyl, halogen, trihalomethyl, CN, NO<sub>2</sub>, OR<sup>10</sup> or NR<sup>10</sup>R<sup>11</sup>,

wherein R<sup>10</sup> and R<sup>11</sup> are independently selected from H, alkyl or trihalomethyl,

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(5) substituted heteroaryl having 1-3 substituents independently selected from alkyl, halogen, trihalomethyl, CN, NO<sub>2</sub>, OR<sup>10</sup> or NR<sup>10</sup>R<sup>11</sup>, wherein R<sup>10</sup> and R<sup>11</sup> are as defined above; or

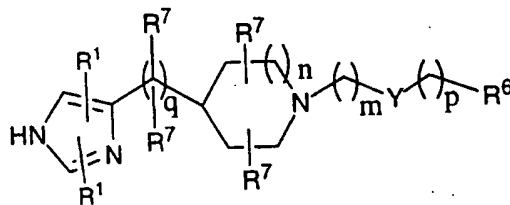
(6) substituted heterocyclic having 1-3 substituents independently selected from alkyl trihalomethyl or NR<sup>10</sup>R<sup>11</sup>, wherein R<sup>10</sup> and R<sup>11</sup> as defined above, said substituents being bound to carbon atoms in the ring such that the total number of substituents in the ring is 1 to 3; and wherein the heterocyclic ring contains substitutable nitrogen atoms, said nitrogen atoms are optionally substituted with lower alkyl;

when Y is -SO<sub>2</sub> -, then R<sup>6</sup>, in addition to the above groups, also represents alkyl having 1 to 7 carbon atoms or a group -NR<sup>10</sup>R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> are as defined above;

each R<sup>1</sup> is independently selected from hydrogen, alkyl or trihalomethyl;

each R<sup>7</sup> is independently selected from hydrogen, alkyl, trihalomethyl, phenyl or benzyl, wherein said phenyl and benzyl are optionally substituted by one to three substituents independently selected from of alkyl, halogen, trihalomethyl, CN, NO<sub>2</sub>, OR<sup>10</sup> or NR<sup>10</sup>R<sup>11</sup>, wherein R<sup>10</sup> and R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> as above defined.

2. The compound of Claim 1 having the formula



wherein:

q is 1 to 7;

m is 0 to 4;

n is 0 or 1;

p is 0 to 4;

when m is 0 to 4, Y is selected from -SO<sub>2</sub> -, -SO<sub>2</sub>NH-, -CONH-, -CO-, -C(NH)NH-, or -CO(CH<sub>2</sub>)<sub>w</sub> O-; and

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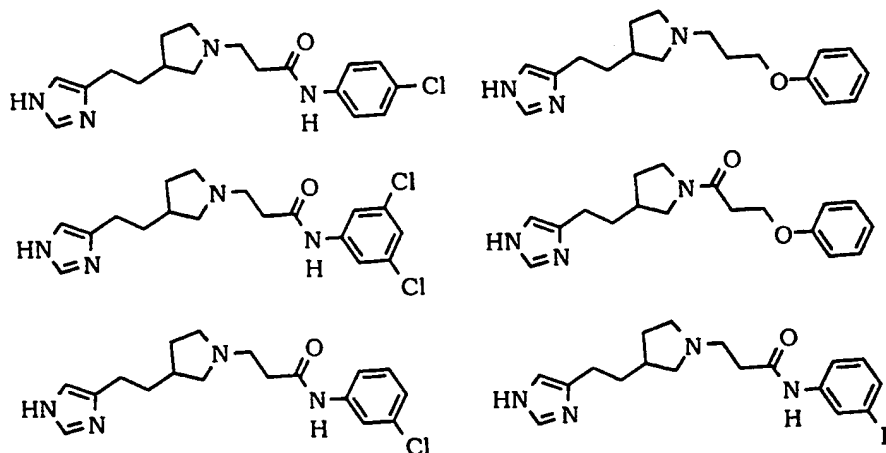
when m is 2 to 4, Y represents all the groups above when m is 0 to 4 and, in addition, Y represents -NHCONH-, -O- or -NHC(NH)NH-; and w, R<sup>1</sup>, R<sup>6</sup>, and R<sup>7</sup> are as defined above.

5           3.     The compound of Claim 2 wherein q is 1 to 4; m is 0 to 3; p is 0, 1 or 2; Y is -CONH-, -SO<sub>2</sub>- or -CO-; R<sup>6</sup> is phenyl or substituted phenyl; each R<sup>1</sup> is independently selected from H or alkyl; and each R<sup>7</sup> is independently selected from H or alkyl.

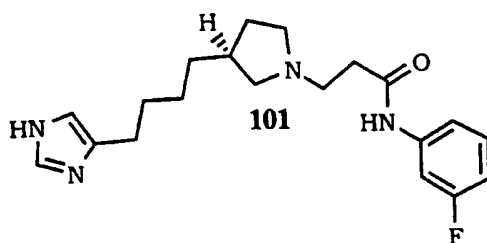
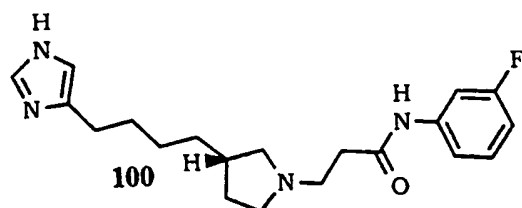
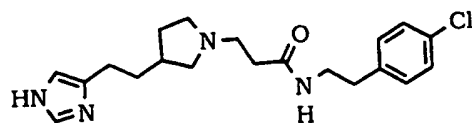
10           4.     The compound of Claim 3 wherein (1) n is 0; (2) Y is -CONH- or -SO<sub>2</sub>-; (3) R<sup>6</sup> is (a) mono-substituted phenyl wherein said substituent is in the 3- or 4-position and said substituent is selected from fluorine, chlorine, methoxy or trifluoromethoxy, or (b) disubstituted phenyl wherein said substituents are in the 3,5-positions and said substituents are the  
15           same and are selected from fluorine, chlorine, methoxy or trifluoromethoxy; and (4) R<sup>1</sup> and R<sup>7</sup> are H.

5.     The compound of Claim 4 wherein q is 2.

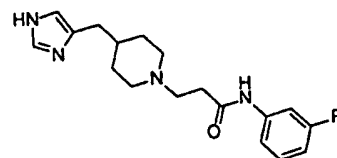
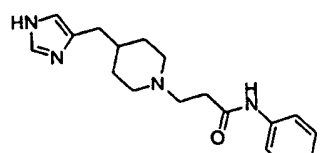
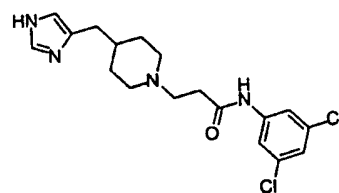
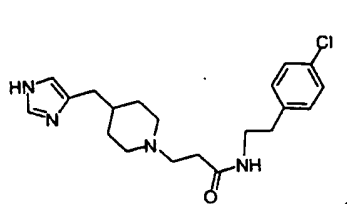
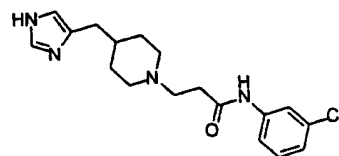
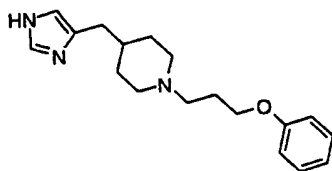
20           6.     The compound of Claim 1 selected from:



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5



10

or

7. The compound of Claim 2 wherein n is 1; Y is selected from



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-SO<sub>2</sub>-, -CONH-, -CO-, or -CO(CH<sub>2</sub>)<sub>w</sub> O-; and, when m is 2 to 4, Y in addition to the above groups, is also selected from -NHCONH- or -O-.

8. The compound of Claim 7 wherein (1) q is 1 or 2; (2) n is 1;  
5 (3) m is 0 to 3; (4) p is 0, 1 or 2; (5) Y is -CONH- or -SO<sub>2</sub>-; (6) R<sup>6</sup> is (a) mono-substituted phenyl wherein said substituent is in the 3- or 4-position and said substituent is selected from fluorine, chlorine, methoxy or trifluoromethoxy, or (b) disubstituted phenyl wherein said substituents are in the 3,5-positions and said substituents are the same and are selected  
10 from fluorine, chlorine, methoxy or trifluoromethoxy; and R<sup>1</sup> and R<sup>7</sup> are H.

9. The compound of Claim 8 wherein q is 2.

10. A pharmaceutical composition comprising a  
15 pharmaceutically acceptable carrier and an effective amount of a compound, or a salt or solvate thereof, of Claim 1.

11. A method of treating allergy, inflammation, cardiovascular  
20 disease, hypotension, glaucoma, sleeping disorders, diseases of the GI tract, states of hyper and hypo motility of the gastrointestinal tract, disturbances of the central nervous system, hypo and hyperactivity of the central nervous system, Alzheimer's, schizophrenia, obesity and migraines comprising administering an effective amount of a compound, or a salt or solvate thereof, of Claim 1 to a patient in need of such  
25 treatment.

12. A method for treatment of upper airway allergic responses comprising administering a compound, or a salt or solvate thereof, of Claim 1 in combination with a histamine H<sub>1</sub> receptor antagonist.

30

13. The method of Claim 12 wherein said H<sub>1</sub> antagonist is selected from: loratadine, descarboethoxyloratadine, fexofenadine, cetirizine.

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14. The method of Claim 13 wherein said H<sub>1</sub> antagonist is selected from: loratadine or descarboethoxyloratadine.

15. The use of a compound, or a salt or solvate thereof, of Claim 1 for the manufacture of a medicament for use in treating allergy, inflammation, cardiovascular disease, hypotension, glaucoma, sleeping disorders, diseases of the GI tract, states of hyper and hypo motility of the gastrointestinal tract, disturbances of the central nervous system, hypo and hyperactivity of the central nervous system, Alzheimer's, schizophrenia, obesity and migraines.

16. The use of a compound, or a salt or solvate thereof, of Claim 1 for the manufacture of a medicament for use in combination with a medicament manufactured for use as an histamine H<sub>1</sub> receptor antagonist, said combination for use in the treatment of upper airway allergic responses.

17. The use of Claim 16 wherein said H<sub>1</sub> antagonist is selected from: loratadine, descarboethoxyloratadine, fexofenadine, cetirizine.

18. The method of Claim 16 wherein said H<sub>1</sub> antagonist is selected from: loratadine or descarboethoxyloratadine.

19. The use of a compound, or a salt or solvate thereof, of Claim 1 treating allergy, inflammation, cardiovascular disease, hypotension, glaucoma, sleeping disorders, diseases of the GI tract, states of hyper and hypo motility of the gastrointestinal tract, disturbances of the central nervous system, hypo and hyperactivity of the central nervous system, Alzheimer's, schizophrenia, obesity and migraines.

20. The use of a compound, or a salt or solvate thereof, of Claim 1 in combination with a an histamine H<sub>1</sub> receptor antagonist for the treatment of upper airway allergic responses.

# INTERNATIONAL SEARCH REPORT

Intern. Application No  
PCT/US 98/23224

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D401/06 C07D403/06 A61K31/445 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| X          | WO 95 06037 A (VRIJE UNIVERSITEIT )<br>2 March 1995<br>see claims  | 1-11                  |
| X          | WO 93 12107 A (SCHERING CORPORATION)<br>24 June 1993<br>cited in the application<br>see page 45, line 16 - page 49, line 23;<br>claims | 1-11                  |
| X          | WO 93 12108 A (SCHERING CORPORATION)<br>24 June 1993<br>see claims   | 1-11                  |
| P, X       | WO 98 06394 A (SCHERING CORP)<br>19 February 1998<br>cited in the application<br>see the whole document                                | 11-14,<br>16-18, 20   |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

3 February 1999

Date of mailing of the international search report

12/02/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
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Fax: (+31-70) 340-3018

Authorized officer

Henry, J

# INTERNATIONAL SEARCH REPORT

Inter. ational application No.

PCT/US 98/ 23224

## Box I Observation where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-14, 18  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 11-14, 18  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No

PCT/US 98/23224

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s)   | Publication<br>date  |
|---|---|---------------------|--|--|
| WO 9506037                                | A | 02-03-1995          | AU 7823894 A<br>NL 9302045 A   | 21-03-1995<br>16-03-1995   |
| WO 9312107                                | A | 24-06-1993          | AT 140223 T<br>AU 665604 B<br>AU 3275893 A<br>CA 2126086 A<br>DE 69212164 D<br>DE 69212164 T<br>DK 619818 T<br>EP 0619818 A<br>ES 2089782 T<br>GR 3021195 T<br>HK 31097 A<br>JP 7121938 B<br>JP 6511252 T<br>MX 9207392 A<br>NZ 246434 A<br>ZA 9209785 A                               | 15-07-1996<br>11-01-1996<br>19-07-1993<br>24-06-1993<br>14-08-1996<br>05-12-1996<br>25-11-1996<br>19-10-1994<br>01-10-1996<br>31-12-1996<br>21-03-1997<br>25-12-1995<br>15-12-1994<br>01-06-1993<br>27-02-1996<br>21-06-1993                             |
| WO 9312108                                | A | 24-06-1993          | AT 141269 T<br>AU 671092 B<br>AU 3277393 A<br>CA 2129679 A<br>DE 69212844 D<br>DE 69212844 T<br>DK 618913 T<br>EP 0618913 A<br>ES 2090956 T<br>GR 3021464 T<br>HK 31397 A<br>JP 7121939 B<br>JP 6511009 T<br>MX 9207393 A<br>NZ 246441 A<br>SG 44510 A<br>US 5463074 A<br>ZA 9209788 A | 15-08-1996<br>15-08-1996<br>19-07-1993<br>24-06-1993<br>19-09-1996<br>09-01-1997<br>14-10-1996<br>12-10-1994<br>16-10-1996<br>31-01-1997<br>21-03-1997<br>25-12-1995<br>08-12-1994<br>30-06-1994<br>27-02-1996<br>19-12-1997<br>31-10-1995<br>22-06-1993 |
| WO 9806394                                | A | 19-02-1998          | AU 3973397 A   | 06-03-1998   |